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EDITORIAL

Ligation of The Internal Mammary Arteries

Dame Fashion dictates the raiment of the individual. There was a time when the requisite of fashion may well have exceeded the concepts of reason. Today the surgical approach to the treatment of cardiac lesions has become quite the fashion. For this reason, the editorial board of SOUTHWESTERN MEDICINE is availing itself of the opportunity of presenting the editorial, "Ligation of the Internal Mammary Arteries", published in the New England Journal of Medicine Volume 257, August 22, 1957, Number 8, Page 385. The Editorial board wishes at this time to express their sincere appreciation to the Editor of the New England Journal for allowing the use of this editorial.

The history of surgical attempts to bring a new blood supply to the heart muscles of patients with coronary-artery insufficiency has a close parallel with earlier attempts directed at the femoral artery. The ligation of veins, the creation of arteriovenous fistulas, the surgical creation of myxedema and the division of sympathetic nerves supplying the arteries have been used in both conditions. Patients presenting themselves for relief of coronary insufficiency are so numerous, and the implications of failure of relief in many of them so great, however, that the types of operation that have been performed on the heart are even more varied than those on the lower extremity. The implantation of tissues bearing vasculature, the plunging of a pulsating and bleeding artery into myocardial tissue, the creation of pericardial adhesions and attempts to augment, by irritating epicardial substances, intercoronary anastomoses have placed the myocardium in a class by itself as an object of surgical assault.

Objective Evaluation

Objective evaluation of the results of these operations has been difficult. Initially, each of them is followed by partial or complete relief in more than half the cases. "Functional" tests are often improved also. Such tests, however, are known to be affected by factors other than the arterial blood supply to the myocardium.

It is safe to say that examination of experimental and clinical evidence and of thoughtful medical opinion indicates that the relief afforded by these operations may not be the result of increased myocardial blood supply. It may rather be the relief experienced by an apprehensive and disabled person who has had his confidence restored by surviving such an operation and who has recognized in his new status as a "post-operative" patient an honorable reason for limitation of activities.

The most implausible operation of all now demands evaluation. The hope that ligation of the internal mammary arteries will, by stimulating collateral circulation via intercostal and pericardial branches, cause increased myocardial blood supply is based on a hypothesis having no physiologic background in hemodynamics. But the announcement is made that the operation, like its predecessors, has relieved many patients of angina pectoris.

Mortality Close To Zero

The procedure admittedly promises to have one conspicuous advantage — namely, a mortality that should be close to zero. For this reason, patients will be more readily referred to surgeons than in the past. The word "surgeons" is used advisedly, rather than "thoracic surgeons" or "cardiac surgeons." But why, after all, "surgeons" of any kind? Cannot any practitioner of medicine, with the aid of procaine and a few instruments, undertake it? And then how about prophylactic ligation? And what might happen to Blue Shield in its attempts to pay for the amount of work involved?

In light of these considerations, what should be the current attitude toward internal-mammary-artery ligation? In the forefront of choices should be the decision for this operation to be done only by those, if any exist, who believe they have at hand proper objective measures for the determination of coronary blood flow with which to evaluate the results of their work.

Edited by Andrew M. Babey, M.D., Las Cruces, N. M.

APHORISMS and MEMORABILIA

Truths and Concepts Concerning The Cardiovascular System

(Continued)

37. "It is a mistake to diagnose pericardial effusion in rheumatic heart disease except on the very strongest evidence available."—CAREY COOMBS, *Rheumatic Heart Disease*, Wm. Wood & Company, Baltimore, 1924, page 252.

38. The *character* of the heart sounds whether first or second, is on occasions of great help in the diagnosis of cardiac conditions, but the idea that one can gauge the functional efficiency of a heart by the *loudness* of sounds is altogether fallacious." —J. LINNELL AND W. A. R. THOMPSON, *Brit. Med. Jour.*, 2: 442, 1938.

39. "Contrary to current teaching, a systolic murmur at the mitral area is the commonest murmur in mitral stenosis, not a presystolic."—J. LINNELL AND W. A. R. THOMPSON, *loc. cit.*

40. "Nocturnal dyspnea may be due to pulmonary infarction."—PAUL WHITE, *loc. cit.*, page 491.

41. "In many cases of angina pectoris both the physical and the electrocardiographic examination are entirely negative."—FRANK WILSON, *Association of Life Insurance Medical Directors of America*, 24: 96, 1937.

Bad Reputation

42. "The very bad reputation which low-voltage complexes have acquired rests upon studies carried out in hospitals where a large percentage of low-voltage complexes are [of abnormal shape as well as size]. Electrocardiograms in which the ventricular deflections are small but normal in every other respect are not necessarily of serious import." —FRANK WILSON, *loc. cit.*

43. "No statistical study is available which gives an adequate idea of the frequency of P-R intervals of 0.21 and 0.22 second in the electrocardiogram of persons who appear to be in good health, but I believe that they are not extremely uncommon, and I doubt that they have any serious prognostic significance."—FRANK WILSON, *loc. cit.*

44. "On the whole, a prolonged QRS interval is a considerably more reliable sign of cardiac disease than a prolonged P-R interval."—FRANK WILSON, *loc. cit.*

Significance Doubtful

45. "It is doubtful whether electrocardiograms which appear to be normal apart from the small size of the QRS deflections have an important significance unless the reduction of voltage is extreme."—FRANK WILSON, *loc. cit.*

46. "It is my impression that conspicious right axis deviation after the age of 40 is almost always abnormal."—FRANK WILSON, *loc. cit.*

47. "Pericardial friction sounds often change from hour to hour, and may disappear and reappear in the course of a day."—RICHARD CABOT (source uncertain).

48. "Systolic and presystolic murmurs at the apex of a very large heart may have little significance."—RICHARD CABOT (source uncertain).

49. "When the pericardial friction sound is single, auscultation may fail to distinguish it from a valvular murmur, and especially so when the single friction sound is heard most distinctly over the situation of the valves."—THOMAS ADDISON'S WORKS, *New Sydenham Soc.*, London, 1868, 36: 65.

50. "So far as auscultation is concerned, the double friction sound of pericarditis if heard toward the base of the heart might be mistaken for the see-saw murmur of imperfect aortic valves or vice versa. The character of the pulse alone would be almost sufficient to decide the question."—THOMAS ADDISON'S WORKS, *loc. cit.*

51. "In certain diseases of the heart, especially when the organ is enlarged it is difficult or impossible, accurately to localize the murmurs, however distinct or obvious these murmurs may be."—THOMAS ADDISON'S WORKS, *loc. cit.*

"POINTERS"

From the Case Records of the Massachusetts General Hospital, 1955*

(continued)

23. "Diverticula with or without evidence of diverticulitis occasionally bleed profusely. I recall seeing a patient who had repeated episodes of massive gastrointestinal bleeding for which no cause could be found. At the time of exploration a small diverticulum of the ascending colon, which contained a fecalith, a large eroded blood vessel and a blood clot, was found. That patient has had no bleeding since the diverticulum was removed six years ago." loc. cit.; p. 152

24. "Massive bleeding from the gastrointestinal tract of obscure origin had better be treated conservatively unless there is a definite indication for operation such as a demonstrable source for the bleeding or to save the patient's life. We have all seen these patients subjected to an exploratory laparotomy in which every inch of the bowel and the entire abdominal contents are examined thoroughly and yet nothing is found." loc. cit.; p. 153

25. "Perhaps we do not think of Meckel's diverticulum often enough; two per cent of autopsies show a Meckel diverticulum. I had not been aware of this extraordinary frequency of Meckel's diverticulum in the whole population." loc. cit.; p. 153

26. "Friedlander's pneumonia, of course, is a rare form of pneumonia; it occurs primarily in older people, particularly those debilitated by age or by chronic alcoholism. Its onset is somewhat different from that of ordinary penumococcal pneumonia. It frequently begins, as this man's illness began, with a chronic bronchitis producing signs and symptoms of pneumonia." loc. cit.; p. 253

Salt Wasters

27. "Patients with pulmonary disease, usually pulmonary tuberculosis, are termed "pulmonary salt wasters." Frequently such patients are suspected of having Addison's disease, but tests of their adrenal functions are normal." loc. cit.; p. 293

28. "Patients with miliary tuberculosis may have no clinical signs of meningeal involvement, and yet analysis of the spinal fluid may reveal an increased number of cells, with no other findings. If this cerebrospinal fluid is allowed to stand, a pellicle may form, and this can be stained and examined for acid-fast bacilli." loc. cit.; p. 293

29. "Patients who receive chlorpromazine should have tests for bile in the urine while they are being treated." loc. cit.; p. 381

30. "Jaundice due to chlorpromazine may be of abrupt onset usually after two or three weeks of therapy; laboratory tests show no hepatic cell damage, only evidence of biliary obstruction. Jaundice may last many months." A composite; loc. cit.; p. 382

Massive Hemorrhage

31. "We have occasionally seen massive hemorrhage, particularly along the lesser curvature, from ulcerations caused by long-standing intubation of a patient." loc. cit.; p. 385

32. "Even though the liver edge was palpable, from the film I cannot be sure of any hepatic enlargement. I think we are much more reliable in the evaluation of the size of the spleen than we are of the size of the liver." loc. cit.; p. 428

33. "A physician years ago said that there are only two kinds of pus in the chest—'thank God pus' and 'my God pus'." loc. cit.; p. 472

34. "That he had a gastrectomy is of particular interest in view of the increasing numbers of postgastrectomy patients in whom pulmonary tuberculosis develops." loc. cit.; p. 570

35. "I believe that a semiannual chest file should be obtained for an indefinite period in the postgastrectomy patient, just as in the follow-up study of the diabetic patient, who is known to be more susceptible to tuberculsois." loc. cit.; p. 570

36. "Upward gaze is the most difficult movement for the eyes to make. Downward gaze is the easiest." loc. cit.; p. 612

37. "At times, however, it is possible for cor pulmonale to exist with very little visible increase in the size of the right ventricle." loc. cit.; p. 655

*We are grateful to Dr. Benjamin Castleman, Editor of "Case Records" and Dr. Joseph Garland, Editor of "The New England Journal of Medicine" for permission to publish these excerpts. They will appear regularly and cover the years 1951 through 1955. —Andrew M. Babey, M. D.

MEETINGS

ATTEND THE
ANNUAL MEETING
of the
SOUTHWEST
OBSTETRICAL
and
GYNECOLOGICAL
SOCIETY
in
Las Vegas, Nevada,
November 4 and 5

Surgeons To Hold Dallas Meeting

A three-day Sectional Meeting of the American College of Surgeons will be held in Dallas, Texas, January 9 through 11, 1958, in the Statler Hilton Hotel.

Topics to be covered range from Chemopallidectomy for Parkinson's Disease to Bomb Phenomenology, as well as panels, symposia and motion pictures dealing with highly practical day-to-day problems confronting busy practicing surgeons. A one-day program in ophthalmology will be held the second day.

Dr. Frank H. Kidd, Jr., Dallas, Assistant Clinical Professor of Surgery, Southwestern Medical School of the University of Texas, is Chairman of the Local Advisory Committee on Arrangements.

Cancer Seminar Scheduled In Tucson Jan. 23-25

Specialists from five states have accepted invitations to participate in the sixth annual cancer seminar of the American Cancer Society in Arizona, to be held in Tucson Jan. 23-25.

Chairman of the seminar committee is Dr. Darwin W. Neubauer of Tucson. Committee members are Dr. Arthur Present, Dr.. Hermann S. Rhu, Jr. Dr. Ralph Fuller and Dr. James Fritz, all of Tucson and Dr. Edward Bregman and Dr. James Barger of Phoenix.

The three-day meeting, to be held at the Tucson Inn, will include lectures by leading authorities in the various fields relating to cancer. Approximately 500 persons are expected to attend. The seminar is open to all physicians and surgeons, internes, nurses and dentists. Last year's seminar, held in Phoenix, was attended by 400.

Panel of Specialists.

The panel of specialists includes Dr. Axel N. Arneson, onconological gynecologist of St. Louis, Mo.; Dr. James Barrett Brown, plastic surgeon also of St. Louis; Dr. Vincent P. Collins, College of Medicine at Baylor University, Houston, Texas; Dr. Ross Golden, diagnostic radiologist of the Medical Center, University of California at Los Angeles; Dr. Cornelius F. Lehmann, dermatologist of San Antonio, Texas; Dr. Ian G. MacDonald, onconological surgeon of Los Angeles, Cal.; Dr. Arthur Purdy Stout, Pathologist of Columbia University, College of Physicians and Surgeons, New York City; and E. Dale Trout, Ph.D., physicist for the General Electric Co., in Milwaukee, Wisconsin.

Opening the seminar program will be a session on skin tumors, scheduled for the morning of Jan. 23. Participating will be Doctors Brown, Collins and Lehman.

That afternoon Doctors Brown, Collins, Golden, MacDonald and Stout will take part in a panel on cancer of the head and neck.

"The Abdominal Mass" will be the subject of a session on the morning of the second day, with Doctors Golden, MacDonald, Stout and Collins participating. That afternoon the subject will be pelvic tumors with Doctors Arneson, Collins and Stout the speakers.

There will be two subjects for the final morning session. Opening the meeting will be a talk by Dr. Trout on "The Application, Limitation and Dangers of Radiation Therapy." The seminar will conclude with a panel on "End Results and Complications," with Doctors Arneson, Brown, Collins, MacDonald and Stout participating.

AMERICAN FRACTURE ASSOCIATION MEETING HELD IN EL PASO, SEPT 30-OCT. 2

FRACTURE MEETING—Attending the annual meeting of the American Fracture Association in El Paso, Texas, September 30 through October 2, were, left to right, Dr. H. W. Wellmerling, Bloomington, Indiana, secretary-general; Dr. Duncan C. McKeever, Houston, president; Dr. W. Compere Basom, El Paso, program chairman; Dr. Homer H. Stryker, Kalamazoo, Mich.; and Dr. Roger Anderson, Seattle, Wash. Drs. McKeever, Basom and Anderson were among speakers at the meeting, which was coordinated with the El Paso Division meeting of the Texas Postgraduate School of Medicine directed by Dr. Ralph H. Homan of El Paso. Both meetings were excellently attended.

IN EL PASO—Among officials and speakers attending the American Fracture Association meeting in El Paso were, left to right, Dr. Garrett Pipkin of Kansas City, Missouri, Dr. Louis W. Breck, El Paso, and Dr. I. William Nachlas, Baltimore, Maryland, speakers; and Dr. Manuel Carrasco, right, president of the Chihuahua City Medical Society in Mexico. Following the Fracture meeting, a group enplaned for a postgraduate session in the Medical University at Guadalajara, Mexico.

United States and Mexico Medical Society To Meet in Tucson Dec. 5-7

The Medical Society of the United States and Mexico will hold its annual meeting Dec. 5-7 at the Santa Rita Hotel in Tucson. Registration will begin Dec. 4.

Officers of the society are: Dr. H. E. Thompson, Tucson, president; Dr. H. G. Guevera, Mazatlan, Sinaloa, president-elect; Dr. W. R. Manning, Tucson, vice-president; Dr. J. E. Fonseca, Tucson, secretary for the United States; Dr. A. L. Guevara, Guadalajara, Jalisco, secretary for Mexico; Dr. R. E. Hastings, Tucson, treasurer for the United States; Dr. R. M. Alvarez, Mazatlan, treasurer for Mexico.

Members of the coordinating committee are Dr. H. E. Thompson, Dr. H. G. Guevara, Dr. J. Chavez, and Dr. W. R. Manning.

THE PROGRAM

Thursday, Dec. 5, 9-11 a.m. meetings of the committees on education, Governors', editing, contagious diseases; 11-12:30 a.m. executive committee meeting; 12:30-2 p.m. luncheon for members and wives with style show; 2-5 p.m. general assembly.

Friday, Dec. 6, 9-12 a.m. scientific assembly; 12-2 p.m. luncheon; 2-5 p.m. scientific assembly; 6:30-8 p.m. social hour; 8 p.m.-1 a.m. dinner dance.

Saturday, Dec. 7, 10-12 a.m. executive committee meeting, tour of Davis Monthan Air Force Base, tour of the University of Arizona, recreation, golf; 6 p.m. social hour, auxiliary dinner and show.

General Practice Review Scheduled in Denver

A full week's general practice review will be held Jan. 13-18 at the University of Colorado Medical Center, 4200 East Ninth Avenue, Denver 20. Postgraduate credit will be given.

Each of the six days will be devoted to a special subject, medicine, pediatrics, surgery, laboratory medicine and radiology, obstetrics and gynecology, trauma.

The course has been designed especially for the general practitioner. Physicians may register for all subjects or any selected one.

For detailed program and further information write the Office of Postgraduate Medical Education, University of Colorado Medical Center, 4200 East Ninth Avenue, Denver 20.

Radiological Safety Course Offered By New York University

A two-week, full-time course in "Radiological Safety" will be given from January 6 to 17, by the Institute of Industrial Medicine of New York University Post-Graduate Medical School, in cooperation with the NYU College of Engineering and the United States Atomic Energy Commission.

The course is designed for industrial physicians, industrial hygiene engineers, public health officials, and individuals in industrial and university research laboratories who are responsible for radiological safety.

Particular attention will be given to radiation problems in Industry associated with the use of radioisotopes and radiation sources including industrial X-ray and power reactors. Covered will be such topics as nuclear physics, the biological effects of radiation, the principles of radiation protection and governmental codes and regulations.

Tuition for the course is $90.

For further information write to the Associate Dean, NYU Post-Graduate Medical School, 550 First Avenue, New York 16, N.Y.

Coming Meetings

Southwest Obstetrical & Gynecological Society, Annual Meeting, November 4 and 5, Las Vegas, Nevada.

United States and Mexico Medical Society, Annual Meeting, Santa Rica Hotel, Tucson, Arizona, Dec. 5-7, 1957.

Radiological Safety Course, New York University Post-Graduate Medical School, 550 First Ave., New York 16, Jan. 6-17, 1958.

American College of Surgeons Sectional Meeting, Statler-Hilton Hotel, Dallas, Texas, January 9-11, 1958.

General Practice Review, University of Colorado Medical Center, 4200 E. 9th Ave., Denver, January 13-18, 1958.

American Cancer Society, 6th Annual Seminar, Tucson Inn, Tucson, Arizona, January 23-25, 1958.

Texas State Surgical Society, El Paso, Texas, April 5-8, 1958.

Fifth International Congress of Internal Medicine, Sheraton Hotel, Philadelphia, April 24-26, 1958.

CURRENT THERAPY

Epilepsy and Its Management

By R. J. BENNETT, M. D., *El Paso**

This is a review of the more recent literature on the subject of epilepsy. The paper follows more or less the organized writings of Penfield, Jasper, Gastault, Lennox and other well known authorities on the subject..

Epilepsy has always been a challenge to the diagnostic accumen of the medical man, for it can demonstrate itself explosively in a form easily recognized, then again it can present such bizarre symptoms that many cases go undiagnosed, the patient either being treated for a neurosis, mental deficiency, character disorder, psychosis or for many and varied physical complaints.

Metabolic Disease

Epilepsy has been described by William G. Lennox as a metabolic disease. Some individuals are born with a low convulsive threshold. They have an inherited susceptibility to various noxae, which in them help trigger epileptic attacks. These noxae may be of hormonal, traumatic, toxic, infectious, allergic, emotional or sensory origin.

Susceptibility to attacks is found in cases of symptomatic as well as idiopathic epilepsy.

This conclusion is drawn from the study of patients who have suffered severe concussions, skull fractures and evidently brain contusions who show comparatively slight residual symptoms without convulsions; yet other patients with mild concussions will develop definite epileptic symptoms. Three chemical substances are thought to be involved in the neurophysiologic disorder, namely glutamic acid, acetylcholine and potassium.

Gradual Change

In recent years there has been a gradual change in the classification of epilepsys from grand mal, petit mal, psychomotor and focal epilepsy. They have been divided into two general groups.

The cryptogenic (or idiopathic), general epilepsy for which no cause has yet been found; and the symptomatic epilepsy for which some lesion or factor is known as a cause (brain tumor, cicatrix, atrophy, circulatory disturbances, etc.). In both groups the attacks are further classified as focal, local and partial epilepsies.

To treat epilepsy most successfully one must recognize the type of attack the patient is having. As mentioned above there are many types of epileptic attacks.

A review of these is pertinent at this time. Grand mal and petit mal of generalized epilepsy have been classified as centrencephalic seizures by Jasper and Penfield. The pattern of the generalized epilepsy is well known and needs no detailed description except for some variations of petit mal attacks which may go unrecognized.

Activities Automatic

There are some petit mal attacks in which the patient may not lose total contact but his activities are automatic. The repetitious acts of children (head nodding, stumbling, inattention etc.) may be petit mal attacks. In others there may be apparent confusion such as failure to recognize familiar objects, places or use of implements.

In relation to petit mal, children suffering from this type of attack are distractible and thought to be mentally retarded, because of their lack of attention and failing work. Others may show restlessness and irritability.

They need more than the usual amount of supervision and correction because of their erratic behavior. Frequently these children are diagnosed and treated as "behavior" problems, the basic cause not being suspected.

Frequent Breaks

The rapid and frequent breaks in the continuity of their consciousness causes marked disturbance in their behavior. The handling of such children by severe disciplinary measures, as if in punishment for willful acts, will aggravate the condition. The attacks are usually of brief duration and may have very frequent recurrence.

These may be automatism. Attacks of similar type but of more prolonged duration are classified as partial epileptic seizures. The partial seizures are those most frequently undiagnosed, for in many the motor or sensory system may not be involved, but only those of associative and autonomic functions.

*Dr. Bennett this month is substituting for Dr. Jack A. Bernard, regular conductor of this section.

The somato-sensory seizures of the partial epilepsies may cause such symptoms as numbness in various areas, paraesthesias, loss of sense of position of a limb, etc. In this group are the visual seizures which may be manifested by scotomas, total blindness, various shaped size and colored moving lights. The olfactory seizures, also called uncinate fits, are those in which various odors are experienced.

Gustatory Fits Rare

Gustatory fits are rare. In the auditory seizures a great variety of sounds may be experienced. There are also virtiginous attacks, usually described by the patient as "dizziness." In all of these types of epileptic seizures, unless the individual suffers from more than one variety, the march of symptoms usually follows the same pattern.

The Jacksonian type of seizure is classified as a focal motor seizure. Other motor seizures are the grand mal, the versive seizures in which the body may end up in a complete rotation. The tonic seizures may be of extensor or flexor type causing opisthotonos or emprosthotonos.

Psychical Seizures: In these are experienced hallucinations and/or illusions. The latter may affect only one special organ. The patient may visualize distortion of objects; they may seem close and gigantic or distant and microscopic.

Hearing may be distorted in a similar manner, sounds being loud and near or faint and distant. There are dream state seizures in which the patient has the illusion of being completely detached from his environment and may express his feelings as those of being a "spectator" watching the stream of life passing by.

There are illusions of recognition or memory also known as de'ja vu de'ja entendu phenomena, in which the person feels he is experiencing an event which had taken place before, as if in a former life. There is an opposite illusion in which the person fails to recognize familiar surroundings.

Hallucinations of psychical seizures differ from illusions in that they occur without external stimuli. A patient described a scene of his childhood in which he was going out to bring the cows from pasture for milking. The setting was always the same with one sister sitting on a fence and the other going to the hen house.

Automatism: These attacks are also known as psychomotor and temporal epilepsy. As the name implies the individual acts automatically. During some of these attacks the patient outwardly may appear to act normally but he is lacking in understanding and as in many other types of epileptic attacks has usually no recall of his actions.

In most cases automatism is easily recognized for the actions are abnormally repetitious, such as smacking the lips, chewing movements, swallowing, growling, clearing throat, handling of objects and self. All of this is done in a purposeless manner.

Dangerous Epileptics.

Some individuals in this state are receptive to directions and handling, but others are dangerous if handled and will fight with the fury of a wild animal.

The person involved in a struggle with this type of epileptic may well be fighting for his life as the latter has no inhibitions and apparently feels no stress.

Some attacks are limited to the speech area (aphasic seizure). The patient not understanding and not being able to think of words or he may be able to think and understand but cannot speak.

Autonomic seizures: The attacks may be sensory or motor or both and involve any part or parts of the autonomic nervous system. Most frequently the G.I. tract is affected.

Symptoms may be vague feelings of discomfort, sometimes described as rising from the abdomen to the throat; nausea, spasms, vomitting, borborigmus, errucatations, etc. Circulatory symptoms give rise to pre-cordial pains and tachycardia.

Respiratory seizures may cause respiratory arrest or polypnoea, the subject feeling he is suffocating. Sweating, pallor, flushing, pupillary changes and pilmotor erection are also experienced in autonomic seizures.

There are some types of seizures which Penfield has placed under the heading of unclassified attacks.

These are status epilepticus, described as frequently recurring attacks with variation in time between attacks, but usually the seizures occur in almost continuous manner and may be followed by confusion, post epileptic psychosis, paralysis or death.

Pyknolepy: Is described as a petit mal-like seizure but holds a better prognosis. It begins between the ages of 4-12. The attacks are frequent, of short duration, follow the same pattern and stop spontaneously and do not recurr.

Akinetic Seizures: In attacks of this type the patient falls suddenly and remains motionless. Usually there is loss of consciousness. Gastaut and Pelligrin are of the opinion that myoclonus may be the cause for the patient's fall rather than the loss of muscle tone.

Epilepsia Partialis continua: In the motor variant local convulsive movements occur which continue over long periods of time, except for short interruptions. There is seldom much spread of the seizure. There are also continuing sensory and psychical auras..

Sensory Precipitation: (Reflex epilepsy). Apparently stimulation can set off epileptic discharges. These may be precipitated by sudden sound (startled precipitation) photic stimulations, certain types of sounds and other sensory stimuli (intercourse, etc.).

Sensory Arrest: While certain stimuli can precipitate an attack, counter stimulation can sometimes abort a seizure. Similarly there are psychic precipitation and psychic arrest. These are brought about by certain types of thinking and concentration. Patients who are aware of an impending seizure by a certain change in thought contents can sometimes avert the seizure by forcing their thoughts into other channels.

Cases have been reported in which transient paralysis may take place in an extremity in which focal motor seizure usually occurs. The so-called epileptic equivalents are now thought to be attacks of epileptic automatism and therefore true epileptic seizures.

There are many unsuspected epileptics whose only complaints may be one or a combination of some of the following symptoms: cyclical vomiting, recurrent headaches, recurrent abdominal pain, "fainting spells," recurrent nightmares, sleep walking, attacks of pyrexia, sweating and enuresis.

Psychosis in epilepsy: This may occur following a seizure or a series of seizures. It is particularly so of fugues, furors and clouded states. However, the condition may come on without necessarily following this pattern.

The psychotic episodes may be the epileptic attack. Such was the case in a patient who was frequently jailed because of his assaultive behavior. This was caused by the onset of auditory hallucinations in which he heard people insulting him.

He would attack the persons whom he thought were tormenting him. Then again the psychosis may take the form of a Schizoid reaction frequently paranoid in type, or it may mimic other types of psychosis.

Epileptic personality: The question whether such exists has long been a point of controversy. There are certain characteristics of personality associated with epileptoids, namely egocentricity; a domineering attitude and general sadistic tendency.

Because of this the individual is at a constant odds with his environment and hard to manage. He is opinionated; boastful; responds poorly to suggestions and authority; does not seem to learn by experience and is irritable. Not infrequently he has a paranoid or psychopathic make up.

Diagnosis: The importance of a thorough history has been mentioned. A neurological examination should be done; an electroencephalogram should be obtained. The latter procedure helps confirm one's diagnosis when positive findings are obtained and is valuable in localizing a focus and in revealing the type or types of seizures the patient is suffering.

It is helpful in determining the choice of drugs or other procedures one needs to follow. One must not forget however that the EEG is only a diagnostic tool and that only 85 per cent of Epileptics will give a positive tracing between attacks.

Clinical Examination

One must still depend on a thorough clinical examination rather than rely solely on diagnostic gadgets. There are various methods of stimulating epileptic tendencies in those who give normal tracings; intermittent photic stimulation is one. Others are opening and closing the eyes; overbreathing; metrazol stimulation alone or combined with photic stimulation and activation by sleep. Routine skull x-rays should be done; and, where indicated angiography, pneumoencephalography, ventriculography and laboratory tests such as glucose tolerance; blood calcium and thyroid function, etc. should be performed.

Treatment

The treatment will depend on the type of seizures and the ability of the patient to cooperate. Most cases will be treated medically and from the office. Those having automatism of violent nature, psychotic reactions as ictal reactions and psychosis need to be confined to a closed ward; and, if these reactions are repeated frequently or fail to clear within a reasonable time under adequate treatment, the patient should be committed to a state hospital.

The Medical Treament: Besides chemical treatment supportive therapy such as dietary, recreational, occupational and psychotherapy can be very helpful and must not be overlooked. As men-

tioned before the epileptic usually has unhealthy personality traits and his handicap creates problems which he must be helped to face.

Medications: In recent years a large number of new and useful drugs have been made available. Prior to that bromides, phenobarbital and the ketogenic diet were the few tools we had. The anti-convulsive drugs most effective in grand mal are: phenobarbital, also called luminal, mebaral, and gemonil in the barbituric acid derivatives; dilantin sodium and mesantoin in the hydantoin derivatives; and mysoline in the primidone and paradione in the dione derivatives.

In petit mal tridone and paradione, milontin and celontin have been found most useful. In the psychomotor attacks, phenurone has been the most effective, but the drug is highly toxic. Patients using it must be examined frequently for untoward effects as it has been responsible for cases of fatal toxic hepatitis. Recently celontin has been made available and is said to have a low toxicity.

Assesory Drugs: Glutamic racemic acid: This has been found beneficial in various types of epilepsy. Some patients with P.M. have been relieved of symptoms by this alone. Amphetamines act favorably in certain forms of epilepsy when combined with anti-convulsant barbiturate derivatives.

Diamox: (Acetazolamide) a carbonic anhydrase inhibitor, which causes a metabolic acidosis similiar to that obtained through the unpalatable ketogenic diet and also causes dehydration through its diuretic action, is a valuable adjunct and at times may be effective by itself (dosage 20mgm./-kg). The addition of promazine or chlorpromazine to anti-convulsive drugs causes further reduction of attacks in some patients and improves their emotional state.

Fitted Drugs

In each case the drug has to be fitted to the type of seizure and to the individual's bio-chemical make up. One may have to change drugs many times before the one suited for each case is found. While it is desirable to keep the individual on one drug if possible, there will be many who need various combinations of anti-convulsants.

The dosage will vary with each individual. Give the minimal amount that will bring results. Abrupt change of drugs is to be avoided. Gradual transfer by first adding the new medication and reducing the old is best to avoid precipitating status epilepticus.

Intake of drugs is most beneficial if small frequent dosage is used to insure steady absorption.

Three To Four Doses

Doses three to four times a day are usually satisfactory. Increase in dosage is warranted when seizures are expected (menstrual, nocturnal, etc). At least a month's trial should be given a new medication.

Close supervision of the patient should be maintained, especially during the first months he is on therapy.

One must watch for untoward drug reactions. Even dilantin sodium and phenobarbital can have toxic reactions. Some of these occur in the form of toxic psychoses. Fatal hepatitis from use of dilantin has been reported.

Hemotologic renal (and hepatic if using phenuron) status should be evaluated before starting the subject on medications.

This should be rechecked in at least a month and should be repeated every three to four months. The patient should be warned that as long as he takes medications he has to be under medical supervision. When the subject has been free of seizures and the EEG has been normal for one to three years, medications may be gradually reduced.

Surgical Treatment

The surgical treatment of epilepsy is reserved for those cases which have failed to respond to medical treatment and which give evidence of having an epileptogenic focus that can be safely removed. Gastaut gives the operative mortality as two to three per cent and therapeutic failures of 35 to 40 per cent. Other measures and regimes which are valuable are avoidance of fatigue, emotional upsets, alcohol intake and constipation. Fluid and salt intake should be reduced to a minimum. The patient should be taught to accept his condition and participate in life's activities as much as his handicap will permit.

Bibliography

(1) **Progress in Neurology and Psychiatry**
Spiegel—Volume X. Grune Stratton. 1955.
(2) **The Biology of Mental Health and Disease**
Paul B. Hoeber, Inc., Harper and Brothers. 1952.
(3) **Masked Epilepsy**
H.R.E. Wallis
E. and S. Livingston, Itd.
Edinburgh and London, Pub. 1956.
(4) **The Engrams of Psychiatry**
Nielson and Thompson
C. Thomas, Publisher.
(5) **The Epilepsies**
Henri Gastaut
Charles C Thomas, Publisher, 1954.
(6) **Epilepsy And The Functional Anatomy of the Human Brain**
Wilder Penfield and Herbert Jasper
Little Brown & Co., 1954.
(7) **The Cyclopedia of Medicine**
F. A. Davies Co. 1954, 1955, 1956
(8) **The Year Book of Neurology and Psychiatry**
McKay, Wortis, Bailey and Sugar. 1954, 1955, 1956
(9) **The Year Book of Drug Therapy**
Beckman 1954, 1955, 1956.

THE PRESIDENT'S COLUMN

Increasing Number of Medical Meetings Brings Competition For Attendance

By Celso C. Stapp, M.D., El Paso

During the past few years we have been seeing a definite change in the attendance at Southwestern Medical Association meetings. This has also been true in similar meetings over the whole country. There are certain definite reasons for this change and there are certain remedies which we will have to seek out to keep our association abreast of times.

Southwestern Medical Association has weathered two wars and the social and economic changes that have gone with it. I am sure that we can continue to progress with our work of dissemination of medical and technical information to our members, with mutual exchange of experiences and problems, thus binding the doctors of the Southwest together and better aquainting them with each other.

Specialty Societies

Since World War II the number of specialty societies and meetings have grown at a phenomenal pace. We have also had the number of prestige organizations growing. The months in the fall and spring are riddled to bursting point with meetings, and all one has to decide is where in the country one wishes to go; and one can tailor the meeting to the occasion and there is bound to be one there. At one time we were unique, as we were the only organization within one day driving in our area to offer a well rounded program.

With the advent of adequate commercial air transportation we are now the meeting that is left. This year the program was excellent and all the papers were presented in a brilliant manner. Still our total attendance was not too good. This means that we are definitely in competition not only with other meetings but with the world series and the flu. What shall we do?

The growth and health of any organization must rest on sound progressive ideas.

We feel that our membership are the people best qualified to give us those ideas.

Ideas Solicited

I urge each and everyone of you to give us those ideas. That is the secret potion which will rejuvenate our meeting and bring our attendance up. Write to the general chairman for the Tucson meeting next year, Doctor H. D. Cogswell, 1602 North Norton Boulevard, Tucson. He is anxious to have your letters telling him what you would like to have. He and his group are formulating their plans, and they would like to have your desires. I for one will be there next year and hope to see you attend and see what changes have been made.

As retiring president I wish to thank you for your help during my term in office and especially those who helped put on the program. The committee chairman and the other workers did a stellar job. Both the scientific program and the social program were excellent and we had no major mishaps. It has been an honor and a pleasure to have been your president, and I commend Doctor Louis Jeckel of Phoenix to you as your new president and a very capable and enthusiastic booster of Southwestern Medical Association.

Conservation in Skin Therapy

Holland, M. H., J. Med. Soc. New Jersey 49:469, 1952

A plea is made for conservatism in treatment of skin disorders. The author sees patients almost daily who have sensitization dermatitis due to use of creams, lotions or ointments containing one of the "—caine" group of anesthetics or the antihistaminics. He prefers Desitin* lotion which contains only the blandest of ingredients. When used in treatment of 100 patients suffering from various types of inflammatory dermatitis, Desitin lotion brought about improvement or complete relief in the majority of subjects without causing true skin sensitization.

**Contains zinc oxide, magnesium carbonate, rose water, lime water and cod liver oil. Supplied by the Desitin Chemical Co.*

Clinical Clippings, January, 1953.

ORIGINAL ARTICLES

Mechanisms of Metastasis and Their Clinical Implications*

By COLIN G. THOMAS, M.D., *Associate Professor of Surgery, University of North Carolina School of Medicine, Chapel Hill*

There is probably no other disease that has been the subject of such broad study by investigators in all fields of medicine and the medical sciences as that of cancer. In addition, allied fields of the physical and social sciences have made significant contributions to the further understanding of this problem. While distinct progress is evident, unfortunately much of the experimental work that is performed by those in purely investigative roles goes unnoticed by the clinician or at times seems to have little practical application. It is therefore necessary from time to time to re-examine some of our concepts of malignant disease in light of the investigative work now underway. This may not only provide the clinician with a better understanding of malignant disease but also permits him to re-examine more critically the current as well as possible practices in the management of these patients.

It is apparent that our concept of malignant disease is changing and concomitantly, there is alteration in our ideas toward prevention and treatment. No longer is all cancer regarded as a progressively malignant tumor that grows relentlessly until death of the host. Duration of the disease and size of the tumor cannot always be quantitatively related to prognosis. Similarly, the histologic appearance may not be an accurate index of the invasive potential of neoplasm.

The recognition that many neoplasms are not strictly autonomous in their behavior is best illustrated by the effect of an altered hormonal environment in carcinoma of the breast,[1] carcinoma of the prostate,[2] and carcinoma of the thyroid.[3] The chemotherapy of various neoplasms is also assuming greater importance not only as a means of treatment but also as a prophylaxis against the growth of disseminated tumor.

We are learning that not only is the biology of a neoplasm important but that in addition, the host and the reaction of the host's tissues are equally important. This is perhaps best expressed by Mc Donald[4] who contends that each cancer has certain biologic characteristics that tend to remain more or less constant throughout its life. In such a case, it is the type of tumor and resistance of the host to that tumor that largely determines the spread of cancer. By the time some cancers can be recognized clinically, they are apt already to have metastasized if capable of doing so. Others may remain local for a long period of time.

It would be well therefore to discuss some of the more recent observations regarding the mechanisms of tumor metastasis and to consider the clinical applications such observations may have. These remarks shall be confined to: **a)** factors known to influence tumor metastasis, **b)** the incidence and significance of blood stream invasion and, **c)** the significance of lymph dynamics in the dissemination of cancer.

Factors Influencing Tumor Metastasis

It is well known that the incidence of metastasis is influenced by factors which may either exert their action directly on the primary neoplasm or act upon the host in such a way that the growth of a metastasis may be enhanced. It is seldom, however, that these points are given emphasis in the management of patients with malignant disease.

In the experimental animal, gentle massage for a period of from two to five minutes over a number of days has been shown to facilitate the dislodgement of tumor cells resulting in pulmonary metastases.[5,6] Carcinoma is apparently much more readily disseminated by this technique than is sarcoma. This massage effect may be a significant but rather uncontrollable factor in the high incidence of metastases from such muscular organs as the tongue, stomach and colon in which there is almost constant activity, simulating this massage effect.

Incision into a tumor has also been shown to be followed by an increased incidence of metastases as well as facilitating direct transplantation. The accidental transplantation of tumor to donor sites of skin grafts done for radical mastectomy wounds as well as the implantation of tumor in abdominal incisions, along needle biopsy tracts, and anastomotic sites are well known clinical examples of this potentiality. In view of the high recovery of neoplastic cells from the washings of operative wounds following radical operations for cancer, it is probable that dissemination, both local and general, is much more common and significant than is realized. The importance of these considerations in the management of malignant disease should be obvious.

*Presented at Southwestern Medical Association meeting in Albuquerque, 1956.

The dissemination of neoplastic cells by factors which act directly on the neoplasm is best explained by the loss of *"adhesiveness"* of cancer cells to one another.[7] This loss of adhesiveness has been shown to be associated with a calcium deficit of the cancer cell and changes in its external surface.[8,9]

Once the neoplastic cell is separate from the contiguous cell mass, its inherent *amoeboid activity*[10] is a most important factor in its invasiveness and ability to metastasize. Spreading factors such as hyaluronidase will also enhance invasion but it has been difficult to demonstrate such factors as playing a dominant role in the human and experimental tumors.

Regardless of the route of dissemination of neoplastic cells, the reaction of the host's tissues at site of arrest will determine the survival and continued growth of the tumor. Although the mechanisms of host resistance are somewhat obscure, we do know that total body irradiation,[11] cortisone, nitrogen mustard, the vital dyes, as well as repeated bleeding may act on the host to enhance the growth of a metastasis.[12] It may be coincidental but all of these agents have in common an inhibitory or suppressing effect upon the reticuloendothelial system of the body.

Incidence and Significance of Blood Stream Invasion

The invasion of a blood vessel by neoplastic cells has long been employed by the pathologist as a criterion of malignancy and is usually considered to be an ominous prognostic finding. Yet, in many circumstances there seems to be little relationship between the demonstration of blood vessel invasion and the life expectancy of the patient. It is now becoming apparent that blood stream dissemination of neoplastic cells is quite common,[13,14] that many or most of these tumor emboli do not survive and that the most important factors in their survival are the conditions of growth as determined by the site of arrest and response of the host. Factors which influence the dissemination as well as the growth of metastases must be considered in planning therapeutic measures for their inhibition or control.

The impression that tumor dissemination by blood stream was relatively uncommon as compared with lymphatic spread was based primarily on the incidence of demonstrable blood stream metastases. In the past few years, however, several investigators have worked out techniques for identifying tumor cells in the blood stream. Perhaps the most extensive work is that of Engell in Stockholm.[13]

In studying various types of neoplasms he found that the demonstration of cancer cells in the peripheral blood was possible but too seldom successful to be of diagnostic value. However, cells in the venous blood draining the region of the tumor were readily identifiable. For example, in 76 patients with carcinoma of the rectum, neoplastic cells were noted in the venous blood in 54 per cent. In 23 patients with metastases at the time of operation or who later developed metastases, the incidence was 65 per cent.

In 48 patients surviving without recurrence, 50 per cent had positive cells so identified. Similar findings were noted in carcinoma of the breast, carcinoma of the colon, carcinoma of the stomach and carcinoma of the lung. It seemed that cancer cells were found with about the same frequency in patients surviving without evidence of recurrence as in those who developed metastases or recurrence.

With the knowledge that hematogenous dissemination of tumor is quite common it becomes even more difficult to explain their location. Some understanding of this problem comes from experimental studies of the location of the Brown Pearce rabbit tumor cells when injected into the left heart of animals.[15] Metastases under these circumstances were found to be distributed on the basis of blood supply. There was not a disproportionate number of tumor cells lodging in those viscera little known for their high incidence of metastatic tumors. However, the viability of the tumor emboli was found to be much greater where cells were arrested in capillaries than arterioles. Thus the many glomerlular loops in the kidney were to be contrasted with the spleen and thyroid for where emboli were arrested primarily in arterioles, they seemed to have greater difficulty in penetrating the wall of the vessel.

Furthermore, the majority of emboli consisted of single cells or small clumps of two to four cells all of which were quite successful in their growth. Sizable clumps did not seem necessary. Further evidence of the importance of the "soil" is that when tumor was implanted into those viscera in which metastases were uncommon, they grew as readily as when innoculated in sites such as kidney and liver.

Prophylaxis in Growth of Disseminated Neoplasm

Observations such as these serve to emphasize the importance of the host as the predominant factor in the growth of tumor emboli. Although surgical trauma may contribute to cell dislodgement and early venous ligation in the field of surgery may prevent further venous dissemination, these are probably relatively unimportant prophylactic measures against the dissemination of carcinoma.

The administration of nitrogen mustard in the early post operative period as a therapeutic agent against embolization that might have occurred antecedent to surgery would seem to be on more rational grounds. Its role would be that of assisting the factor of host resistance against those tumor emboli that have undoubtedly been occurring for some time before the surgical attack on the neoplasm. It would seem likely that the neoplasm at this time would be much more susceptible to such an agent than when it is well established as a growing tumor metastasis.

This is the concept of treatment that has been applied to control local contamination of peritoneal and other surfaces susceptible to tumor implantation. Radioactive colloidal gold has been shown to inhibit the growth of intraperitoneal rat sarcoma.[16] Its clinical application has been best demonstrated in its use after removal of ovarian carcinoma.[17]

It was with this type of prophylaxis in mind that we have been studying the effect of nitrogen mustard administered to mice after inoculating their peritoneal cavity with Erlichs Ascites Tumor.[18] We have been rather encouraged with these experimental observations in that as long as 72 hours following inoculation, the treated animals developed no evidence of neoplasm whereas 100 per cent of the controls developed Ascites tumors. Others have been able to demonstrate similar inhibition when neoplasm has been disseminated by way of the blood stream.[19] Nitrogen mustard in terms of its availability, hazard to personnel and potentials of tissue damage and side effects has many advantages over radioactive colloidal gold for these purposes.

Lymph Dynamics in the Dissemination of Metastatic Neoplasm

The mechanisms of lymphatic involvement by neoplastic cells are probably quite similar to those governing blood stream invasion — requiring an active aggresive cell with amoeboid motion. Why some tumors exhibit a greater potential for lymph vessel invasion and others blood vessel, is not apparent. Certainly, there are more exceptions to what was formerly considered a difference in the behavior of sarcomas and carcinomas than was formerly realized. This again, however, may be primarily an expression of host resistance or anatomical distribution of the vascular channels.

That the lymphatic dissemination of tumor is an active process and not merely a dislodgement of cells into lymph vessels has been demonstrated by injecting tumor cells into the anterior chamber of the eye.[20] Lymphatic metastases do not occur until there is actual invasion of the choroid and sclera. In the tumors studied this occurred as early as the fourth day and lymph node metastases could be seen in all animals by the twelfth day.

Once tumor cells gain access to lymphatics the initial dissemination is primarily an embolic phenomenon. Fortunately, lymph nodes which function as a very effective barrier to the passage of tumor emboli are interspersed between lymph and vascular channels. The efficacy of such a barrier can be examined by injecting V-2 carcinoma into the afferent lymphatics of the popliteal lymph nodes of rabbits.[21]

Excision of such a lymph node up to a period of three weeks — at which time it is nearly completely replaced by cancer — is followed by no further evidence of dissemination. After that time, however, spread to more proximal nodes occurs.

For the most part, there is very little information concerning the factors which may influence the effectiveness of a lymph node as a barrier against carcinomatous spread. The effect of certain systemic agents such as x-ray, cortisone and the vital dyes on suppressing the reticuloendothelial system and inhibiting the resistance of the host to tumor growth has already been mentioned.

In keeping with this general concept is the finding that the presence of a predominantly reticuloendothelial cell pattern ("sinus histiocytosis") in lymph nodes is correlated with a much better prognosis than in patients whose lymph nodes exhibit no such change.[22] This has been demonstrated primarily in neoplasms of the breast, stomach and bowel. Since the administration of choline may be followed by an enhancement of reticuloendothelial cell function,[23] this brings up the very distinct possibility of being to favorably influence the phagocytosis of tumor emboli by regionally situated lymph nodes.

Most of the views on the lymphatic dissemination of cancer have been based on injection studies in the cadaver and the location of metastatic cancer. With a view towards procuring further information as to the dynamics of lymphatic spread, we have been employing radioactive colloidal gold as an investigating tool.[24] Radiogold was selected for use because of its physical and biologic characteristics. It has a safe half life of 2.7 days and its emission spectrum consists of a Beta ray with very little tissue penetration. However, a fairly powerful Gamma ray constitutes about 5 - 10 per cent of the total radiation produced and thereby permits determinations of radioactivity at some distance from the location of the isotope.

It has a particle size of from 50 - 300 millimicrons which permits easy dissemination but still of sufficient size to permit phagocytosis. When injected interstitially, the dissemination of this radiocolloid is primarily by way of the lymphatics and the colloidal particles are phagocytized by the reticuloendothelial cells of the body. Animal and human experiments have disclosed the feasibility of irradiation damage even to the production of complete necrosis in lymphatics and lymph nodes. In these instances, radiogold has been found located in the subscapular and hilar regions of lymph nodes as well as the reticuloendothelial pathways which surround follicles.

In the experimental studies with this isotope, the objectives were threefold; **a)** to determine the predominant pathway of lymph flow from any particular neoplasm; **b)** to investigate the possibility of the therapeutic use of radiocolloids in the management of inoperable lymph node metastases; **c)** to observe any alteration in lymph dynamics in the presence of lymphatic metastases.

Routes of Lymphatic Flow

As a method for determining predominant routes

of lymphatic flow in the human by topographical survey, the use of radiogold is of chief value in those areas of the body which permit broad localization. This can readily be achieved in the extremities, chest and abdominal wall. For example, in the lower extremity a tracer amount of radiogold passes almost immediately to the inguinal lymph nodes with no evidence of interruption by the popliteal lymph nodes. Surveys of the anterior chest wall, both axillary and supraclavicular regions following injections of the breast disclose localization of radioactivity primarily in the axilla.

Activity over the parasternal areas can be easily identified. However, there is sufficient dissemination to the blood stream and phagocytosis by the reticuloendothelial cells of the lung and liver that interpretation is difficult. Perhaps the most significant finding is that of alteration in lymphatic flow. The absence of a predominant lymphatic flow to the axilla connotes rather massive lymphatic replacement by neoplastic cells. Under these circumstances an aggressive surgical attack will be much more likely to disseminate rather than eradicate breast cancer.

Insofar as head and neck carcinoma is concerned, the anatomy of this area does not lend itself as well to such analysis as does the chest wall and it was possible only to demonstrate a general localization of the radiogold in the region of the injection site and homolateral lymph nodes.

In all these studies, most impressive was the immediacy of dissemination. Within a few minutes after injection, colloidal particles could be found in many lymph nodes and at considerable distances from the site of the injection.

Treatment of Lymphatic Metastases with Radiocolloids

The treatment of lymphatic metastases of malignant neoplasms by injection of radioactive colloids has been suggested by several investigators on the basis of the behavior of these colloids when introduced interstitially. In fact, there have been reports advocating the treatment of inoperable metastases of carcinoma of the lung, cervix and prostate by these methods.

The irradiation of cancerous lymph nodes by disseminated radiocolloids would depend upon the ability of these nodes to phagocytize sufficient quantities of the radiocolloids to result in their own destruction. This could occur with only partial replacement of the lymph node by cancer and function of the remaining lymphatic tissue. By studying lymph nodes removed from surgical specimens previously injected with radiogold, it is possible to determine the feasibility of the therapeutic use of this isotope.[25]

Of 593 lymph nodes removed from 35 patients with carcinoma of the breast or head and neck, 374 contained radiogold and 94 contained cancer. The cancer involvement varied from partial to almost complete replacement of the lymph node. Only 33 of these 94 cancerous lymph nodes also contained radiogold. In general, within the same specimen more radiogold was usually present in normal than in cancerous lymph nodes. Furthermore, it was apparent that frequently the "normal" nodes contained no radiogold. This finding was usually associated with the presence of metastatic cancer in other lymph nodes.

Two factors would seem to militate against the effective treatment of carcinomatous nodes by radiocolloids. In the presence of metastatic cancer, there is apparently some alteration in "normal" lymphatic flow as measured by radiogold deposition.

As a result, there is no uniform distribution of radiogold even in those lymph nodes uninvolved by neoplasm. Secondly, and of greater importance, is the failure of gold to be deposited in most lymph nodes containing cancer. From studies of these lymph nodes with the dark-field microscope human cancer does not appear to contain functioning lymphatic channels and therefore, in such nodes lymphoid tissues appear to be essential for a carcinomatous node to phagocytize radiogold. The greater the replacement of the node by tumor, however, the less likely the deposition of gold colloids.

Metastases and Alteration in Lymph Dynamics

Perhaps the greatest value of these studies has been the ability to learn more of lymph dynamics as modified by the presence of malignant neoplasm. It has become quite apparent, for example, that colloid particles introduced into the oral cavity have a very wide dissemination to lymph nodes throughout the neck.

There has been very little evidence of "filtering" by more proximal nodes and quite unexpected was the finding of relatively high counts in nodes that had ordinarily been regarded as out of the field of lymphatic flow. When the base of the tongue was injected, there was quite commonly a high count in the suboccipital group of nodes which have not been stressed as a potential site of metastatic cancer. This has also been true for lesions of the tonsil. We have also noted at times a rather haphazard distribution of carcinomatous lymph nodes from neoplasms situated along the gingival margins, tonsil or tongue. Thus both the clinical findings of metastatic carcinoma as well as the wide spread dissemination of radiogold from the primary tumor sites would support the view that there is no place for limited dissections in the treatment of metastatic cancer involving lymph nodes of the neck.

In contrast to the findings in the breast, the lymph plexus from the oral cavity seems sufficiently great that despite fairly extensive involvement of lymph nodes by metastatic cancer, there is little demonstrable alteration in lymph dynamics. This has also been true in those patients having a bilateral neck dissection for their malignant disease.

Studies in Carcinoma of the Breast

Probably the greatest returns have come from studying patients with carcinoma of the breast.[26] The findings in these individuals have been most helpful in learning more about normal lymphatic flow as well as the progression of lymphatic metastases. The surgical treatment of carcinoma of the breast has been based upon the premise that this neoplasm spreads primarily by the lymphatic rout — a centrifugal embolic spread with progressive chain-like involvement of more lymph nodes. This concept plus the clinical evidence that there may be a segmental type of lymphatic flow from certain areas of the breast, has lead to the extension of surgery beyond axillary node dissection in an effort to include a greater area of potential lymph drainage.

These areas have included supraclavicular, internal mammary and mediastinal lymph nodes. The finding of carcinomatous lymph nodes in these areas of extension has been considered to be justification for this approach. The validity of these concepts, however, has never been carefully scrutinized experimentally since, until recently, most of the views on lymphatic drainage of the breast were based on studies in the cadaver and the location of metastatic cancer. These methods have not permitted a quantitative study of lymphatic flow and it has not been possible to appraise the relative importance of the various routes or under what conditions the accessory pathways may assume greater import.

Furthermore, relatively little attention has been given to the alteration in lymph dynamics that occurs in the presence of metastatic neoplasm. One purpose of this investigation was to make a quantitative study of lymphatic flow from various quadrants of the breast and in particular to appraise any significant alteration in lymph dynamics by the presence of lymph node metastases.

Thirty three patients with breast cancer were studied by these methods. Twenty patients had no evidence of lymph node metastases, and these included eight with internal mammary node dissections. Thirteen patients including seven with internal mammary node dissections were found to have one or more metastatic lymph nodes containing cancer. Of the fifteen patients having an appraisal of their internal mammary lymph nodes, four had carcinoma involving axillary and one or more internal mammary lymph nodes and three had involvement of axillary lymph nodes only. No patient had carcinomatous deposits in the internal mammary lymph nodes alone.

Distribution of Radiogold in the Absence of Demonstrable Metastatic Neoplasm

Regardless of the site of placement of the radiogold, there was usually a generalized distribution in identifiable lymph nodes. Of the 332 lymph nodes examined in these twenty patients, only sixty were not found to contain any radiogold.

Although in some individuals the lymph nodes nearest the injection site contained the greatest concentration of radioactive particles, there were many instances in which the highest node in the axilla or one of the nodes along the lateral portion of the axillary vein or in the region of the subscapular vessels had an equally high count. Considerable variation in counts per node was quite common and this could occasionally but not always be correlated with the size of the lymph node. Lymphatic flow to the internal mammary lymph nodes was merely a trickle as compared with that to the axillary chain. Although a comparison of the gold deposited in axillary and internal mammary lymph nodes is most gross, the internal mammary nodes contained less than one per cent to two per cent of the total radiogold deposited.

Even if it is assumed that the maximum number of internal mammary nodes were present and that the lymph nodes examined were representative, these figures would not be appreciably altered. It was quite clear that injection in any quadrant could be followed by the deposition of gold in the internal mammary chain.

A contributing factor to the relatively minor roles played by the internal mammary lymphatics may be the small number as well as the small size of the lymph nodes present. This would in effect produce a more ineffectual barrier and one that is soon replaced by neoplasm.

From these studies in patients without metastases and employing radiogold as a criterion of lymphatic flow, it is evident that there is very little *segmental* lymphatic flow from quadrants of the breast. All sections drain primarily by way of the axillary lymph nodes, but with some drainage to internal mammary nodes. There was a suggestion that the internal mammary nodes are perhaps relatively more important in receiving afferent lymphatics from the medial portions of the breast. However, even here, lymphatic flow is primarily in the direction of the axilla.

Lymphatic Drainage as Altered by the Presence of Carcinomatous Lymph Nodes

In evaluating the location of lymph nodes as well as the radiogold in patients with one or more lymphatic metastases, several findings were of interest. The presence of carcinoma in the internal mammary lymphatics was always associated with axillary metastases. The location of the axillary metastases did not reflect the location of the primary tumor, although in general, the nodes of Rotter were most frequently involved with lateral quadrant lesions. In several instances what would be considered the nodes nearest the tumor were uninvolved whereas only the apical axillary nodes contained carcinoma. This "skipping" of lymph nodes has also been noted by Monroe.[27]

The presence of carcinoma was associated with a

haphazard distribution of radiogold through the uninvolved lymph nodes, as compared with the distribution in patients without metastases. This irregular distribution of radiogold in uninvolved lymph nodes can best be explained on the basis of lymphatic blockage. There are not a sufficient number of observations, however, to be able to indicate a quantitative relationship between the number of lymph node metastases and alteration in lymph flow.

The presence of extensive axillary lymph node involvement by neoplasm but without any demonstrable lymphedema, results in marked alteration in lymphatic flow such as to the opposite breast, diaphragm or hepatic lymphatics. In these individuals, there may be no demonstrable gold in axillary or internal mammary lymph nodes even though they contain lymphatic tissue as well as carcinoma.

If the dissemination of radiogold can be used as a guide to lymphatic flow from the breast, it is evident that particulate matter in any segment of the breast may pass through any of the lymphatics known to drain breast parenchyma. Despite the clinical evidence that suggests some segmental drainage from the breast, the predominant lymphatic flow from all areas as herein studied, is toward axillary lymph nodes. Less than one to two per cent of lymphatic flow is in the direction of the internal mammary lymphatics. It is likely that other accessory pathways have similar import.

Conditions are quite different and somewhat unpredictable once obstruction of some of the afferent lymphatic pathways occur. Where axillary lymph nodes are extensively involved by cancer, internal mammary, inframammary and all accessory routes of lymphatic flow are utilized. In the presence of axillary lymph node metastases, it is easy to understand the high incidence of internal mammary metastases. Whereas the axilla probably remains a more effective barrier against lymphatic spread of carcinoma because of what constitutes more or less multiple lines of defense, the internal mammary lymph nodes are few, small and probably provide a most ineffective barrier against carcinomatous spread.

These studies would seem to have the following clinical significance. In the absence of lymphatic metastases to axillary lymph nodes, the inclusion of the internal mammary lymphatic chain in an effort to encompass the regional lymph flow from the breast enhances this possibility only by the percentage of lymphatic flow to this area. This probably represents less than two per cent of total lymphatic flow. It is likely but has not been substantiated experimentally that the quantitative flow to this area from medial portions of the breast may be somewhat higher.

In the presence of axillary lymph node metastases, particularly when they occur to such an extent that there is an obstruction in afferent lymphatics and alteration in lymphatic flow, the internal mammary lymphatic chain represents only one of the alternate routes available — many of which are unpredictable. Extirpation of the internal mammary chain under these circumstances would seem to provide a relatively insignificant removal of potential areas of lymphatic drainage.

Summary

To recapitulate, it is evident that some of the factors influencing tumor metastasis can be recognized and there are some over which we may have some control. The realization of the high incidence of direct tumor dissemination during surgical treatment as well as the high incidence of lymphatic and blood stream invasion may be somewhat disheartening to the individual who associates the success of treatment with the aggressiveness of the surgical attack. Yet, such dissemination is not always synonymous with clinical metastasis and serves primarily to emphasize the importance of the host in determining growth of transplanted neoplasm.

Perhaps, more of our investigative as well as therapeutic efforts should be directed toward enhancing this host resistance to the spread of malignant disease. It is just becoming apparent that some of the chemotherapeutic agents may be more than palliative when employed in this manner.

Although for the most part, these observations and findings are discouraging to our present concepts of treatment, they are the facts as we know them. Recognition and consideration must be given to these facts if we are to intelligently employ the best methods of therapy available today.

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References

1. Beatson, G. T. "On the Treatment of Inoperable Cases of Carcinoma of the Mamma: Suggestions for a New Method of Treatment with Illustrative Cases." *Lancet*, 2:104-7, 162-65, 1896.
2. Huggins, C. and Hodges, C. V. "Studies on Prostatic Cancer. I. The Effect of Castration, of Estrogen and of Androgen Injection on Serum Phosphatases in Metastatic Carcinoma of the Prostate." *Cancer Research*, 1:293-97, 1941.
3. Thomas, C. G. "Hormonal Treatment of Thyroid Cancer". *J. Clin. Endocrinol.* In press.
4. MacDonald, I. G. "Biological Pre-Determinism in Human Cancer". *Surg., Gynec. & Obst.*, 92:443, 1951.
5. Tyzzer, E. E. "Factors in the Production and Growth of Tumor Metastases". *J. Med. Research*, 28:309-332, 1913.
6. Knox, L. C. "The Relationship of Massage to Metastases in Malignant Tumors". *Annals of Surg.* 75:129, 1922.
7. Coman, D. R. "Decreased Mutual Adhesiveness, a Property of Cells from Squamous Carcinoma". *Cancer Research*, 4:625, 1944.
8. Coman, D. R. "Mechanism of the Invasiveness of Cancer". *Science*, 105:347, 1947.

9. Coman, D. R. and Anderson T. F. "A Structural Difference Between the Surfaces of Normal and Carcinomatous Epidermal Cells". *Cancer Research*, 15:540, 1955.
10. Enterline, H. T. and Coman D. R. "The Amoeboid Motility of Human and Animal Neoplastic Cells." *Cancer*, 3:1033, 1950.
11. Koletsky, S. and Gustafson, G. E. "Whole-Body Radiation as a Carcinogenic Agent". *Cancer Research*, 15:100, 1955.
12. Baserga, D. and Baum, J. "Induction of Blood-Borne Metastases by Tumor Transplantation in the Tail of Mice". *Cancer Research*, 15:52, 1955.
13. Engell, H. C. "Cancer Cells in the Circulating Blood". *Acta Chir. Scand.* Suppl. 201, 1955.
14. Fisher, E. Turnbull, R. B. "The Cytologic Demonstration and Significance of Tumor Cells in the Mesenteric Venous Blood in Patients with Colorectal Carcinoma". *Surg., Gynec. & Obst.* 100:102, 1955.
15. Coman, D. R. "Mechanisms Responsible for the Origin and Distribution of Blood-Borne Tumor Metastases" *Cancer Research.* 13:397, 1953.
16. Woodward, E. R. and Harper, P. V., Jr. "The Prevention of Peritoneal Tumor Implants by Radioactive Colloidal Gold". *Annals of Surg.* 140:206, 1954.
17. Keetel, W. C. and Elkins, H. B. "Experience with Radioactive Colloidal Gold in the Treatment of Ovarian Carcinoma". *Am. J. Obst. & Gynec.* 71:553, 1956.
18. McDonald, C. T. and Thomas, C. G. Unpublished Data.
19. Cruz, Ernesto P., McDonald G. O. and Cole, W. H. "Prophylactic Treatment of Cancer." *Surgery*, 40:291, 1956.
20. Plenk, H. P. Sorenson, F. M. and Eichwald, E. J. "The Time Interval Between Tumor Inoculation and Metastatic Spread to the Lymph Nodes." *Cancer Research*, 14:580, 1954.
21. Zeidman, I., Copeland, B. E. Warren, S. "Experimental Studies on the Spread of Cancer in the Lymphatic System." *Cancer*, 8:123, 1955.
22. Black, M. M., Kerpe, S. and Speer, F. D. "Lymph Node Structure in Patients with Cancer of the Breast". *Am. J. Pathol.* 29:505, 1953.
23. Heller, J. H. "Stimulation of the Reticuloendothelial System with Choline". *Science*, 118:353, 1953.
24. Thomas, C. G. "The Use of Radiogold in Studying the Dynamics of Lymphatic Dissemination of Cancer". *Surgical Forum of Am. Col. Surg.*, 612, 1954.
25. Thomas, C. G. "Lymphatic Dissemination of Radiogold in the Presence of Lymph Node Metastases". *Surg., Gynec. & Obst.* 103:51, 1956.
26. Thomas, C. G. "Progression of Lymphatic Metastases in Carcinoma of Breast". In press.
27. Monroe, C. W. "The Lymphatic Spread of Carcinoma of the Breast" *Archives of Surgery*, 57:479, 1949.

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The Influence of Emotional Factors on Cardiac Disease

By LOUIS A. SELVERSTONE, M.D., *Physician, New England Center Hospital; Assistant Professor of Medicine, Tufts University School of Medicine, Boston*

This is the fourth of an outstanding series of seven articles covering the effects of emotional stress in the practice of medicine. The articles were prepared for a symposium delivered in January at the Tufts-New England Medical Center in Boston.

SOUTHWESTERN MEDICINE wishes to take this opportunity to express its great appreciation to the Bulletin of the Tufts-New England Medical Center and its editor, Dr. Robert P. McCombs, for making this important series available for publication.

SOUTHWESTERN MEDICINE is proud to have the opportunity to publish the articles comprising this symposium on emotional stress which is believed to be the most complete and thorough discussion of this subject.

Next month: "The Influence of the Emotions Upon the Respiratory Tract," by Robert P. McCombs, M.D., Senior Physician, New England Center Hospital; Professor of Graduate Medicine, Tufts University School of Medicine, Boston.

Traditionally and poetically, the heart has always been considered to be the seat and origin of our emotions. With increasing medical sophistication, however, it becomes necessary to reverse this, to discuss the effects of the emotions themselves upon the heart!

The patient with organic heart disease, like other patients, is subject to the usual storms and stresses of life, and like other patients, adjusts to them as best he can. However, the patient with heart disease bears an additional burden, which is not present to so great a degree in patients with diseases of other organ systems—his fear of his diagnosis. Heart disease is the leading cause of death in America today, and the implications of this fact are not lost upon our patients. This terrifying fear may become the most important aspect of medical management, and may produce more disability than the disease itself.

Terrifying Experience

For even the most stable individual, to be told that his heart is diseased may be a terrifying experience, no matter how gently the news is broken. If the diagnosis is not fully understood, and if the physician's reassurance is only casual, the patient may develop exaggerated fears concerning his prognosis. Even a minor, asymptomatic electrocardiographic abnormality, of no clinical importance, may cause the patient to brood about the future support of his family, about the possibility that he may become a hopeless invalid, and about the possibility of sudden death.

When the patient with heart disease is, to begin with, an insecure and unstable person, the situation is potentially much more serious. With patients of this type, belated reassurance may be completely ineffective. Often the patient believes that the doctor is lying to him when he attempts reassurance. Some patients sink into complete invalidism, capitalizing upon their illnesses, forcing their families to wait upon them hand and foot. Others become negativistic and resistant to therapy, ignoring instructions concerning digitalis and salt restriction. Often they become very hostile, acting as if it were the physician's fault that they are ill. Some develop deep depressions, and suicide is not unknown. Accordingly it is essential that we keep in mind the fact that the diagnosis of heart disease, itself, is one of the most potent emotional influences acting upon the patient with heart disease.

Extremely Susceptible

The fact that the normal circulatory system is extremely susceptible to emotional influences is everyday knowledge. The layman is familiar with the tachycardia and rapid breathing which accompany anger and excitement, with the cold, sweaty palms and cold feet of fear, and with nervous palpitations and nervous syncope. These reflex changes are largely mediated through the autonomic nervous system. As physicians, we are familiar with the reciprocal innervation of the

heart and blood vessels by the sympathetic and parasympathetic nervous systems, represented centrally in the hypothalamus. The emergency role of the adrenal medulla and the endogenous secretion of epinephrine are also familiar stories.

Controlled studies on the physiological effects of anxiety on the human cardiovascular system in recent years have demonstrated profound effects. Hickham, Cargill, and Golden in 1948[1] demonstrated that in the majority of young adult males, anxiety had an effect similar to the administration of small doses of epinephrine. With anxiety, cardiac output increased by 50 per cent, the pulse speeded, the blood pressure rose moderately, but the peripheral resistance decreased. In a small group, however, anxiety resulted in an increase of peripheral resistance and in an elevation of blood pressure with no change or a decline in cardiac output.

Circulatory Collapse

Stead, Warren, Merrill, and Brannon[2] in 1945 showed that in certain people anxiety may be attended by circulatory collapse. The peripheral resistance may decrease, while the usual compensatory increase in cardiac output fails to occur, producing a resultant drop in the blood pressure to low levels. In these patients, the heart rate is slow and there is severe sweating and hyperperistalis, suggesting strong vagal overactivity.

Patients with heart failure usually have fixed cardiac outputs which they cannot increase.[3] As Hickham points out,[1] emotional stress in these patients may cause a marked rise in pulmonary arterial pressure, because of the inability of the left ventricle to increase its output to keep pace with the right ventricle. This is the probable explanation for the production of acute pulmonary edema by emotional stimuli.

Data Confirmed

Numerous other studies have confirmed and extended these data concerning the effects of emotions on cardiovascular response. Soldiers in the front lines have higher blood pressures than rear echelon troops.[4] Many cardiac arrhythmias, including paroxysmal auricular tachycardia, paroxysmal auricular fibrillation, and even ventricular tachycardia[5] have been attributed to emotional effects, mediated through the autonomic nervous system. Even the electrocardiogram is susceptible to emotional influence. The studies of Logue *et al.*[6] and of Magendantz[7] have demonstrated transient T wave changes under the influence of anxiety, which return to normal with rest and sedation.

Considering the complexity of the human nervous system and the impossibility of standardizing the subjective sensation of anxiety, it is not surprising that the effects of emotional stimuli upon the circulatory system are so variable. The important point is that these emotional stimuli have been shown to be capable of producing profound objective effects upon the circulation.

Physiological Effects

The widespread physiological effects of emotional factors upon the circulatory system is nowhere better seen in clinical medicine than in the management of hypertension. Human blood pressure varies from minute to minute, under autonomic control. Every physician has had the experience of finding a markedly elevated blood pressure when first examining a new patient, only to have the pressure fall dramatically after a short rest. In the hospital, one often sees elderly women without evidence of heart disease whose blood pressures on admission may be as high as 240/130. Yet after only a day or two in the hospital, without any medication, their pressures may come down to the normal range.

There is also a large group of patients with so-called "doctor's office hypertension." These patients may show no evidence of cardiac, renal, or electrocardiographic abnormality, yet may have consistently high blood pressures when the physician examines them. Freis[8] has emphasized the fact that examination by a physician may in itself produce sufficient anxiety in patients to raise the blood pressure acutely by appreciable amounts. Accordingly, he recommends that pressures be taken at home, by the patient, or by nurses or technicians. He has shown that pressures so obtained are significantly lower than when they are taken by the doctor himself. It is probable that this group of patients usually have much lower pressures than the doctor detects.

Hypertensive Headaches

Hypertensive headaches are a good example of the influence of emotional factors upon the production of symptoms. Many patients with high blood pressure have headaches, but the true hypertensive headache is a relatively rare symptom. It is characteristically occipital, occurring when the patient awakens in the morning, is often accompanied by nausea and vomiting, and usually disappears after only an hour or so. Most headaches of which patients with hypertension complain are not of this type, and appear clearly to be tension headaches of psychoneurotic origin. Stewart[9] in 1953 found that of 104 hypertensive patients who did not know their blood pressures

were high, only 17 had headaches. In a comparable group of *96* who knew of hypertension, *71* had headaches.

The influence of emotional factors in angina pectoris has been recognized since the first description of the syndrome by Heberden[10] in 1768. Heberden pointed out that angina could be produced by "any disturbance of the mind," as well as by physical exertion. This is easy to understand in the light of Hickham's work,[1] since the increased cardiac output and increased blood pressures caused by emotional excitement together result in increased left ventricular work, producing an increased myocardial demand for oxygen in the presence of a compromised coronary circulation..

Worry Factor

Frequently, in early angina, both physical exertion and emotional unrest must be present before the pain is produced. Last year I saw a Boston businessman whose office was on Beacon Hill. He could not understand at first why he sometimes got angina on walking to his office and sometimes did not, no matter what the weather conditions. On thinking over his problem, however, he spontaneously volunteered that if he worried about business matters on the way uphill, he would usually have to stop because of angina. However, if his mind were occupied with more pleasant topics, he could climb the hill without any anginal symptoms. Worry alone did not produce his symptoms, nor did the exertion alone, but the combination was usually sufficient.

Angina is, of course, a subjective sensation, and the intensity with which the pain is perceived will depend to some extent upon the personality of the patient—upon how stoical or how excitable he may be. When angina increases, particularly if the patient has been told of his diagnosis and told that it is very serious, a vicious circle may be set up. Each attack of chest pain causes severe apprehension, and the apprehension facilitates the appearance of the next seizure. The more frequent the seizures, the greater the apprehension, and hence the seizures may rapidly increase in number. This may soon result in severe angina decubitus. The agitation of these patients may be profound, and their physicians may feel themselves forced to resort to narcotics to control their pain. Sometimes these patients may be helped by strong and firm reassurance, encouragement toward limited activity, and the judicious use of sedative and tranquilizing drugs. While one does nothing for the underlying coronary disease, the relief of the emotional component may produce gratifying relief of incapacitating symptoms.

Psychic Factor

This psychic factor should be kept in mind when evaluating the results of new therapies for angina. It is a common experience that any new drug for angina works well at first, so long as the doctor communicates his confidence in it to the patient. When "double blind" tests are done, however, the medication may appear almost useless.

The results of surgery for angina pectoris should also be evaluated with this point in mind, especially since some surgeons state that patients often have relief by the first day after operation, before any new collateral vessels can be formed. The drama of a surgical operation may be a potent psychotherapeutic factor in these patients, and relief of the emotional component of their angina may produce dramatic relief. This is not to state that surgery is useless in angina, but only to point out that the mere fact that symptoms are relieved does not prove the value of an operation, where there are no controls.

Chief Symptoms

This point of view may also be applied to rheumatic heart disease with valvular damage, though here the chief symptoms are dyspnea and fatigue rather than chest pain. It should be noted that dyspnea and fatigue are also subjective symptoms, like anginal pain.. Patients with valvular damage often have subjective disability superimposed upon their organic impairment. Emotional stress may produce increased pulmonary arterial pressure, and the patient's symptoms may be in part secondary to this functional cause.

It is easy to understand why strong emotional factors are usually present in rheumatic heart disease. Consider, for example, a girl who has had rheumatic fever with valvular damage at the age of 12. Perhaps overprotected by her parents, she is forbidden to play with the other children, and cannot take gym in school. At every physical examination, her physician pauses a long time over her heart, and insists on frequent x-rays and electrocardiograms. With marriage, the doctor warns against pregnancy, and during pregnancy watches her extremely closely. As time goes on she may develop dyspnea and orthopnea. It is not to be wondered that her organic disability is often complicated and made worse by a strong subjective disability, given this background of long-standing apprehension.

This point is made very clear by the following case history. A 36-year-old housewife was admitted to the New England Center Hospital four years ago for consideration of possible mitral valve surgery. She had had two attacks of rheumatic

fever, the first at the age of 12, and the second at the age of 19. During the six years prior to this admission, she had developed severe and progressive exertional dyspnea together with orthopnea and ankle edema. During the year prior to admission, she had had three episodes of hemoptysis. In spite of excellent medical management, her symptoms had increased rapidly, and at the time of admission she claimed to be completely disabled, unable to climb a half flight of stairs or to do any housework. .

On physical examination she was not in acute distress. Her heart was enlarged transversely. There was an apical diastolic thrill and a loud, snapping mitral sound. A long, low-pitched, rumbling murmur filled all of diastole at the apex, ending in a classic presystolic crescendo. There were no systolic murmurs.. The pulmonic second sound was louder than the aortic second sound. No opening snap could be heard. While the lungs were clear to examination, the liver edge was felt two cm below the right costal margin. There was no peripheral edema. .

Laboratory Studies

Her routine laboratory studies were within normal limits. Her electrocardiogram was nonspecific, showing neither right or left ventricular hypertrophy. The P waves were consistent with auricular enlargement. Careful chest x-rays and cardiac fluoroscopic studies were done. There was mild pulmonary congestion and definite right ventricular hypertrophy, together with left auricular enlargement. On fluoroscopy it was felt that there was probably some left ventricular hypertrophy as well as right ventricular hypertrophy, but the right ventricular hypertrophy seemed clearly the predominant lesion.

In her preoperative evaluation, cardiac catheterization was not done. There was general agreement that she presented the classic findings of mitral stenosis together with symptomatology which was both incapacitating and rapidly progressive. There was speculation that she might have some moderate mitral regurgitation to explain her slight left ventricular hypertrophy, but it was felt that she would benefit from relief of her mitral stenosis, and accordingly operation was recommended.

At surgery the surgeon found that the mitral valve had been markedly distorted by rheumatic heart disease to allow free mitral regurgitation. There was no significant mitral stenosis, and the surgeon could pass 2½ fingers easily through the mitral orifice.. A 4+ regurgitant jet was felt. Since nothing could be done for this, the auricle was sewed up and the chest was closed.

When the patient had recovered from anesthesia, it was felt unwise to discourage her by telling her the bad news. She was told only that the operation had gone well and that she would soon feel better. Within a few days she showed startling improvement in her symptomatology. She announced with pride that she was now able to lie flat in bed without several pillows under her head. She quickly became ambulatory and walked throughout the hospital, climbing stairs without dyspnea, telling everyone who would listen how greatly she had been benefited by her miraculous heart operation. She was discharged home very shortly, a happy and grateful patient. During the next two years she maintained a great part of her improvement. She was continued on the same cardiac regimen she had been on before operation by her family doctor, but now was able to do her housework, get around without dyspnea, and even go out dancing with her husband, something she had not done for years. During her third year following surgery, she finally again began to go downhill.

Emotional Relief

To all the physicians who took care of this patient during her hospital stay and who followed her case thereafter, her initial improvement was every bit as dramatic as that seen with patients with tight mitral stenosis whose valves had been adequately fractured at surgery. Her increase in exercise tolerance was of the same order of magnitude, and she was just as grateful to her physicians for her dramatic improvement. Yet all that had actually been done was to make a scar on her chest and to suggest to her very strongly that she was really better! While her objective cardiac disability remained unchanged, her subjective reaction to it was markedly relieved. One can speculate here that the relief of her anxiety relieved her already badly damaged heart of an additional heavy emotional burden, allowing her to experience real and lasting improvement.

It is interesting to speculate how much of the improvement we see in many patients after valvular surgery may not be due to this same mechanism. This is not at all to deny the very real value of mitral valve surgery, but to emphasize the fact that a great deal of the relief in some cases may be relief of functional disease rather than relief of the organic disability. In this connection, it should be pointed out that cardiac catheterization studies before and after mitral commissurotomy have often shown little correlation between the degree of subjective improvement attained by the patient and the change in the objectively measured values of the cardiac output,

pulmonary arterial and pulmonary venous pressures after surgery.[11]

Emotional Stresses

Up to now we have considered some of the special emotional stresses to which the patient with organic heart disease is subjected and the manner in which these emotional stresses act to produce changes in cardiovascular dynamics, and have attempted to illustrate the discussion with a few specific examples. What conclusions may one draw from the foregoing of possible value to the practicing physician?

In the first place it must be realized that one cannot take the patient with heart disease and divide his symptoms into those which are "organic" and those which are "functional," as if the patient's organic disease were "heads" and the patient's functional symptoms were "tails" on a coin. The organic and functional aspects in each patient's case are not separate from each other, but are in constant interaction. The organic disease acts upon the patient's personality, while the patient's personality, at the same time, influences and changes the course of the patient's organic disease. This constant interaction must be kept in mind with every patient, in reaching a diagnosis, in assessing the degree of disability, and in making decisions concerning therapy.

Calm Diagnosis

Since the diagnosis of organic heart disease is in itself such a threat, it is the physician's obligation to do all that he can to minimize the patient's fears, and to avoid causing additional anxiety. When a diagnosis is reached, the patient deserves a calm, careful, full, frank, yet optimistic explanation of his diagnosis, an explanation of the rationale of the treatment decided upon, and a full discussion of the prognosis. It is human nature to fear the unknown, and one can face facts far better than fancies.

It is not necessary, or indeed, desirable, however, to do this all at once on a first visit. The patient at first is often very upset, and it is amazing how outrageously the physician's explanations may be misunderstood by a very nervous patient. This education of the patient can usually be spread out over a series of visits, with careful repetition of important points, using down to earth language that the patient clearly understands.

In addition, we must be constantly on guard against creating additional and perhaps unnecessary fears. Often, we may ourselves be in doubt concerning the significance of a soft murmur, for example, or an asymptomatic electrocardiographic abnormality. It is an excellent rule, under these circumstances, to underdiagnose rather than to overdiagnose. In the long run, less harm results from a postponed correct diagnosis than from an erroneous diagnosis that one must later withdraw.

While examining the patient, it is important to realize that he is watching the doctor constantly, for what he doesn't say as well as for what he does say. The physician may have a grave face because of personal problems. The apprehensive patient may, however, misinterpret this as evidence that the doctor considers his case a very serious one. It is necessary constantly to be on one's guard against inadvertent slips, which may lead to misinterpretation.

Unnecessary Restrictions

In treatment it is important to guard against unnecessary restrictions, since the patient often interprets each restriction as additional evidence of the seriousness of his disease. Not every patient with heart disease requires a low salt diet, nor is exercise restriction necessary or desirable in many children with asymptomatic murmurs. The patient with mild hypertension without evidence of vascular disease is usually better treated with simple reassurance than with complicated schedules of hypotensive drugs. Especially with children, it is essential to protect the child against parental overprotection, since the child's whole life may be warped by excessive and unnecessary restrictions.

Finally, with appreciation of the role of emotional stress in the production of the symptoms of organic heart disease, one may also develop a most desirable skepticism toward dramatic new therapies, until they are backed by complete objective data, including proof that subjective factors have been controlled. With each new therapy, rigorous scientific proof backed by complete and adequate controls must be insisted upon.

BIBLIOGRAPHY

1. Hickman, J. B., Cargill, W. H., and Golden, A. Cardiovascular reactions to emotional stimuli. Effect on the cardiac output, arteriovenous oxgyen difference, arterial pressure, and peripheral resistance. *J.Clin.Investigation* 27:291, 1948.
2. Stead, E.A., Jr., Warren, J.V., Merrill, A.J., and Brannon, E.S. The cardiac output in male subjects as measured by the technique of right atrial catheterization. Normal values with observations on the effect of anxiety and tilting. *J.Clin.Investigation* 24:326, 1945.
3. Hickman, J. B., and Cargill, W.H. Effect of exercise on cardiac output and pulmonary arterial pressure in normal persons and in patients with cardiovascular disease and pulmonary emphysema. *J.Clin.Investigation* 27:10, 1948.
4. Pickering, G.W. High Blood Pressure. New York. Grune & Stratton, 1955, p. 215.
5. Ring, A., and Blankfein, J. Paroxysmal ventricular tachycardia in an apparently normal heart. *Ann.Int.Med.* 42:680, 1955.
6. Logue, R.B., Hanson, J.L., and Knight, W.A. Electrocardiographic studies in neuro-circulatory asthenia. *Am.Heart J.* 28: 574, 1944.
7. Magendantz, H., and Shortsleeve, J. Electrocardiographic abnormalities in patients exhibiting anxiety. *Am.Heart J.* 42:849, 1951.
8. Freis, E.B. Recent developments in the treatment of hypertension. *Med.Clin.North America* 38:1 (March), 1954.
9. Stewart, I. Headache and hypertension. *Lancet* 1:1261, 1953.
10. Heberden, W., quoted in Classic Descriptions of Disease, by R.H. Major. Springfield. Charles C Thomas, 1955, p. 420.
11. Grissom, R.L., Pascale, L., Creticos, A.P., and Selverstone, L.A. Analysis of successes and failures after mitral valve commissurotomy. Proceedings of the Section on Clinical Cardiology of the American Heart Association, 1954, p. 17.

MONTHLY CLINICAL PATHOLOGICAL CONFERENCE
EL PASO GENERAL HOSPITAL

September 19, 1957

FREDERICK P. BORNSTEIN, M.D., EDITOR — Case No. 824

Presentation of case by William I. Coldwell, M.D.

History: — Dr. Nathan Kleban

A 64 year old painter was referred to this hospital by his doctor on January 27, 1957, because of anemia.

Severe weakness, aching of the legs, and anorexia were noted one month before admission. His wife thought he was very pale two weeks later. Syncope and vomiting each occurred once. There was an estimated seven pound weight loss. Chills, fever, jaundice, black stools, known loss of blood from any body opening, palpitation, shortness of breath and cough were denied.

Past history was not significant. There were no known familial blood disorders.

Physical Examination:

The patient was a pale, slightly jaundiced Latin-American man who looked chronically ill. Temperature was 99.0, pulse 100, respirations 20. Blood pressure was 130/70. Lymph nodes 1-2 cm. in diameter were felt in the neck, axillary and inguinal regions. Some felt matted. The liver edge was felt through a thick abdominal wall about three cm. below the right costal margin.

Hospital Course:

In addition to blood examinations there were two bone marrow aspirations, two lymph node (axillary) and a skull biopsy. There was a low grade undulating fever for the first and last two weeks with other sporadic slight rises. Twelve units of blood were given. ACTH was given for four days. Metacorten, 20 mg., later 80 mg., daily, was prescribed from Jan. 30 until death. Tetracycline was administered from Feb. 4 to March 14.

The patient felt much better late in February, was using a walker to go to the bathroom and had a good appetite in early March. Swelling of the neck and face in the region of the jaw angles with throat pain was present from March 18 to March 23 which subsided without treatment.

He again ate well until March 31 when he began to refuse his food, appeared despondent and voiced a feeling of hopelessness. He began to complain of abdominal pain, had loose green stools in bed, became confused, disoriented, restless. He died on April 4, the 66th hospital day, with hypotension and a black stool prior to death.

Laboratory Findings:

X-ray: February 4: Chest, ribs and skull: "Conclusions: Skull, findings suggestive of possible myeloma. There are lesions in the frontal area. Chest and thoracic spine show no significant changes."

Biopsies: February 4: Bone marrow—crest of ilium — "Erythroblastic hyperplasia."

February 4: Axillary lymph node: granulomatous lesion of undetermined type. Fig. 1. Note — Special stains for acid-fast organisms and fungi are negative."

February 14: Bone marorw (skull)— "Sections show numerous fragments of bone tissue and fibro-connective tissue. No tumor is seen."

March 25: Axillary lymph node: "Malignant lymphoma, type undetermined. Note: The changes in the lymph node compared to the previous biopsy show the presence of a progressing lesion which has features suggestive of Hodgkin's disease or reticulum cell sarcoma. In view of the bone changes the possibility of so-called 'histiocytosis X' has to be considered. I do not believe that this represents either a plasmocytoma or a chloroma."

Blood counts: Jan. 27: Hb. 4.8 gms; Ht. 11 per cent; segs. 85; lymphs. 15; wbc, 19,900

Jan. 28. Hb. 3.5 gms, Ht. 12 per cent; Segs. 73; lymphs. 16; stabs. seven; juveniles two; monos; two; total wbc 22,200
Jan. 28: (after 1000 cc. whole blood): hb. 5.0 gms.
Jan. 30: Hb. 5.0 gms.
Jan. 30: rbc 1.49
Jan. 31: Hb. 6.9 gms.
Feb. 15: Hb. 4.6 gms. Ht. 15 per cent.
Feb. 25: Hb. 8.6 gms.
Mar. 14: Hb. 10.7 gms. Ht. 35 per cent; wbc 9,000; Segs. 81; lymphs. 12; monos. two; stabs. five
Mar. 22: Hb. 12.3 gms. Ht. 40 per cent; wbc 5,900; segs. 62; lymphs. 28; stabs. nine; juveniles one

Urinalysis: Jan. 27 —S. G. 1.026—acid, sugar and albumin negative, 2-3 wbc, occ. renal ep. cells—many coarsely granular casts, many motile bacteria, some mucus.

Sedimentation rate: Jan. 28—60 mm.
Serology: Jan. 29: negative.

Blood chemistry: Jan. 28: blood sugar — 118 mg per cent
Total protein — 9.2 gm. per cent
Albumin — 4.6 gm. per cent
Globulin — 4.6 gm. per cent
A/G — 1/1
Urea Nitrogen — 28.2 mg. per cent
Van den Bergh direct — .6 mg. per cent
Indirect — 2.75 mg. per cent.

RBC fragility test: Jan. 30—beginning hemolysis 0.69 per cent — complete hemolysis 0.27 per cent

Coombs test: Jan. 30—negative.

L-E cells: Feb. 2—No LE cells found.

Bone marrow aspiration: Feb. 1—"Morphology of the bone marrow reveals an erythroid hyperplasia compatible with acute hemolytic anemia. There is no evidence of tumor cells or blood dyscrasia."

Axillary node culture—March 26—B. micrococcus.

Prothrombin time—Jan. 28—39 per cent.

Coagulation time—4 minutes—bleeding time one minute—Jan. 28.

X-Ray Discussion — Dr. Vincent Ravel:

We have here the views of the chest and skull. We were asked to ascertain whether or not there were any osteolytic or osteoblastic lesions which could be in the nature of a malignancy. As far as the ribs and the thoracic vertebrae are concerned, we were unable to identify anything in the nature of a myeloma or reticulum cell sarcoma or leukemia of any of the lymphoblastomas that sometimes make their presence known by changes in the bony architecture.

When we came to the skull we noticed that there were certain irregular radiolucencies in the frontal region which could be venous lakes or which could be changes such as are seen in a multiple myeloma. The reason that we favored a multiple myeloma was that there is no bone reaction about the site of the radiolucencies.

No Bone Reaction

One of the characteristics of a multiple myeloma when seen in the bone is that it does not produce bone reaction. Metastatic carcinoma, even though it may produce osteolytic changes, nevertheless will show osteoblastic changes around the periphery, and this lesion does not. The remainder of the skull showed no significant changes.

The pineal could not be identified and we do not see any of the secondary signs of increased intracranial pressure, so radiographically we have little to contribute except the suggestion that this may turn out to be a myeloma. From the radiographic standpoint we have very meager evidence to suggest anything that might be pathognomonic in the skull.

Chest Films

The chest films are not the usual six foot roentgenograms which we usually see and it would be very difficult to evaluate the mediastinum. Certainly the trachea is not displaced, and whether or not the hilar vessels could be considered more prominent than usual I wouldn't want to say. The films were in the recumbent position. The diaphragms are somewhat elevated, and I would be a little reluctant, on the basis of this technique, to say that there is any hilar adenopathy.

Clinical Discussion — Dr. William I. Coldwell:

On the announcement card sent out by the hospital it said "CPC by D.W.I. Coldwell". I assure you I am cold sober tonight. In this case the presence of anemia makes one, of course, think of lead poisoning of a chronic nature in a painter.

Nothing further was done in the way of proving this and certainly the subsequent findings did not bear out this possibility. This patient had jaundice, weakness, hepatomegaly and, most significantly, lymphadenopathy. In the differential diagnoses of enlarged lymph glands there are, first, acute infections.

In this group are acute localized lymphadenopathy, including the ones associated with local infections. There is, of course, the generalized lymphadenopathy which may be found in such diseases as infectious mononucleosis and certain acute contagious disorders.

Chronic Enlargements

Chronic lymph node enlargements primarily are those of tuberculosis and the mycoses. Of course, the allergic reactions may produce lymphadenopathy, such as serum sickness which we often get following penicillin reactions.

Congenital abnormalities can be dismissed here. The leukemias of course commonly produce lymph node enlargements. Certain metastatic malignant lesions, of course, do. Here it doesn't appear to represent that sort of condition.

It seems that we are dealing with the so-called primary lymph node disorders which include the lymphosarcomas, reticulum cell sarcomas, the giant follicular lymphoblastomas and Hodgkin's disease. Biopsy of these nodes apparently showed a malignant lymphoma mentioned previously by Dr. Bornstein.

Pathological Interest

As to the specific type involved, this seems to be primarily one of pathological interest. This group of primary lymph node disorders is usually indistinguishable one from the other clinically. The lymph node enlargement is usually localized at first. Later it is often disseminated.

The glands are usually discrete and firm in the early stages. In this patient they were somewhat matted. They are often asymmetric, as opposed to leukemia which produces generally symmetricaly lymph node enlargement.

Infectious Origin

Tenderness usually suggests an infectious origin. However, in Hodgkin's disease if they enlarge rapidly, they also may be tender. A rubbery firmness is noted in most of these primary lymph node disorders. In Hodgkin's, they often become almost cartilaginous in texture.

Hodgkin's often causes enlargement of the inferior posterior cervical group which is rarely involved by infections in the throat region.

In this case the exact location, and actually the exact nature, of the glands is not mentioned in the history. I think it should be mentioned, it should be noted in the history and on the physical examination.

Fever of a low grade type, as was seen here, is often present in this group of diseases, especially in Hodgkin's. The typical Pel-Ebstein fever of course was not present. It is not found very often.

It may have been that this patient was given enough cortical steroids to control most of the fever in the later stages.

Palpable Liver

The liver is often palpable in these disorders, as we noted here. Weight loss occurred and this patient had already lost weight prior to his admission to the hospital. In these conditions many different systems are often involved.

Here the gastro-intestinal system seemed to be prominent. The patient I believe died as the result of a terminla gastro-intestinal hemorrhage. In X-ray, as Dr. Ravel has mentioned, areas of rarefaction are often seen.

Sometimes a diffuse bone marrow involvement is present. Certainly here bone marrow involvement was not present, as least in the areas that were examined, and the skull biopsies by Dr. Stratemeyer failed to show any tumor or any other involvement of this type.

Blood Affected

These lymph node disorders usually affect the blood picture and certainly here the blood was affected very definitely. Anemia is often present, it is usually normocytic in type, but here appeared to be hemolytic. This patient on admission had a very severe anemia.

The history of blood loss was absent as I mentioned in the past. There was an increase in the serum bilirubin. There was leucocytosis.

The serum bilirubin increase was chiefly of the indirect type, which would favor a hemolytic type of anemia.

A negative Coomb's test was present. There was apparent increase in the mechanical fragility of the red blood cells, and an erythroblastic hyperplasia of the bone marrow.

Normoblastic

I presume this was normoblastic; it was not mentioned which it was. No mention was made of

reticulum cells or of mitotic figures which one quite commonly sees in hemolytic anemia in the bone marrow.

No tumor or cell infiltration was noted in the bone marrow punctures. No report was made on the urine and fecal urobilinogen, which should have been increased. No mention was made of reticulocytosis or thrombocytosis.

The latter findings are common with hemolytic anemias. Transfusions were given at the start with little benefit to the patient; there was almost no response in the blood picture until steroids were given.

There was no mention made as to any reactions following transfusions.

Hemolytic Anemia

Certainly with hemolytic anemia one would expect some hemoglobinuria, increased jaundice or other evidence of a reaction unless, I believe, in one instance some packed cells were used instead of whole blood.

The leucocyte count was elevated. This often occurs in Hodgkin's disease alone and the presence of hemolytic anemia in addition would possibly indicate that both factors were operative here.

Neutrophilia was present which is also usual in both conditions. After steroid therapy the blood picture showed a definite improvement which again would favor hemolytic anemia.

As stated before, this case falls into the malignant lymphoma group. Attempts to sub-divide these interrelated tumors on the basis of rigid histologic criteria have resulted in a rather confused nomenclature which serves only to cloud the facts.

Some pathologists and even some clinicians attempt to make a differential diagnosis between these various disorders in this group. They seem to feel that it makes a great deal of difference as to what diagnosis is made.

Actually, it doesn't make too much difference; they are all malignant tumors which vary only in the degree and type of differentiation.

Histologic Criteria

You are probably familiar with Jackson and Parker's classification of Hodgkin's on the basis of the histologic criteria as to paragranuloma and granuloma or sarcoma. The paragranuloma supposedly affects the blood picture very little and apparently is a less malignant form of Hodgkin's.

The Hodgkin's granuloma is the typical Hodgkin's disease which you are familiar with and the sarcoma is almost the same as the reticulum cell sarcoma, both pathologically and clinically similar to these conditions.

Actually, there are many transitions between these different forms, and between these and the follicular lymphoblastoma, lymphosarcoma and even between some of the chronic lymphatic leukemias which have affected the peripheral blood very little.

Variations Seen

Variations are seen in both the clinical and the pathologic pictures between the various conditions in the same patient in various stages of his disease and even in the same patient at the same time when nodes are taken from different areas.

At any rate, this classification to me seems very artificial and confusing, perhaps Dr. Bornstein can illuminate the field with some newer and more confusing concepts, as he has already mentioned. For those of us in the practice of medicine the attempts to classify these disorders seems rather futile.

Our main concern is to be able to make the diagnosis from this general group and to be able to apply the types of therapy we have available. These consist of surgery first.

If there is definite evidence of localization of the nodes, certainly radical surgery should be done if at all; and in some instances where hypersplenism may be present, as it often is in these cases, splenectomy may help alleviate that.

Irradiation of course can be used if dissemination has occurred and also may be used locally after radical surgery of nodes if we think we are dealing with a localized disease.

Too often we find that it has already been disseminated prior to surgery. The final form of treatment available is chemotherapy, and here the old stand-by of course is nitrogen mustard and of that group.

We have used nitrogen mustard for a number of years in Hodgkin's mostly. It seems to help them a great deal.

It may be used when they become radio-resistant, usually after a waiting period of about six weeks. You are familiar with the dosage, .4 to .6 mg. per kilo in the use of nitrogen mustard.

We have also TEM, triethylenemelamine, essentially an oral mustard, and another drug, Lukoran, which is put out by B & W. Co. and was used in a few cases of this group with varying degrees of success.

Arthur Grolman has used colchicine, three mg. IV every three days for three weeks and it achieves some results. It apparently is a mitotic poison.

In this case the steroid hormones were used rather extensively. I think with little effect on the basic course of the disease, but it did help the hemolytic anemia, as mentioned before.

Certainly none of these drugs can be expected actually to alter the course of these conditions.

They decrease the toxicity of the patient, make them feel better and allow them to live a little more pleasant life during their remaining days.

In this case the supportive therapy included a lot of antibiotics.

I don't know just why so many antibiotics were used, they certainly have no effect on the conditions. The patient apparently had no real infection, but in the case of infections, they are indicated.

Of course transfusions were used here in large quantities.

Only Justification

In the prognosis of these conditions lies actually the only justification for using the pathologist's classification because certainly if the tumor is more differentiated, in the more differentiated group, one can say possibly that there is a litttle better prognosis.

However, to us in the practice of medicine, I think the most important thing is the response to therapy.

If the patient responds rapidly to therapy, if he apparently goes into a long remission, one can certainly say that the prognosis is fairly good.

If they have a prompt relapse or if the disease spreads soon after treatment, we can't give much of a prognosis, or much of a favorable prognosis.

The course of the disease is so variable we must use all of our available therapeutic methods, use them as early as possible, knowing, of course, that we are dealing with none that are actually curative. In this case certainly the therapy was, I consider, very discouraging.

In summary, the diagnosis that I have made is: (1) Malignant lymphoma of the Hodgkin's sarcoma or reticulum cell sarcoma; (2) Hemolytic anemia secondary to number one; (3) Terminal gastro-intestinal hemorrhage.

Clinical Diagnosis: Malignant lymphoma

Pathological Diagnosis: Hodgkin's disease of lymph nodes, spleen, bone marrow and intestinal tract.

Pathological Discussion—Dr. Frederick P. Bornstein:

On autopsy we found the body of a well developed, elderly white man. The skin and sclerae had an anemic appearance. The gross examination as a whole was not too impressive. Palpable lymph nodes were found, specially in the mediastinal, retro-peritoneal and mesenteric regions. Some of the lymph nodes showed a grayish-white, glass-like cut surface. Other lymph nodes were composed of gritty tissue.

The liver was not remarkable. The spleen weighed 350 grams which represents a moderate enlargement. However, the cut surface showed the usual splenic pattern.

The most outstanding gross pathologic change was found in the small intestine. The mucosa was edematous, swollen and this was specially prominent along the region of the Peyer's patches (Fig. 2).

On microscopic examination these lymph nodes, small intestine and spleen showed a rather typical picture composed of a mixture of large reticuloendothelial cells and Sternberg giant cells (Fig. 3). In many places the picture blended into that of a reticulum cell sarcoma. However, as a whole it was too pleomorphic.

As was noted in the history, this patient suffered from a severe hemolytic anemia, which may be explained, at least in part, by the appearance of the bone marrow.

The normal substance of the bone marrow on microscopic examination revealed an extensive replacement of the bone marrow by small granulomatous nodules (Fig. 4) which had the same histological pattern as was found in the lymph nodes, spleen and intestine.

In short, the autopsy showed an extensive Hodgkin's disease which included severe damage to the bone marrow.

To answer Dr. Coldwell's question about the classification of the malignant lymphomas and its practical value, I would like to remind you that the differential diagnosis of congenital lesions of the heart was at least as academic as the present classifications of lymphatic diseases, but in the meantime has become of extreme practical value.

I still believe that in a teaching institution we should spend considerable effort at arriving at a precise and accurate diagnosis even if it will not influence the course or treatment of the disease.

It is my personal feeling that there exist close inter-relations between the lymphatic leukemias and various lymphoblastomas.

Furthermore, in one group of lymphoblastomas cells will be produced which resemble Sternberg giant cells and these tumors therefore are called Hodgkin's sarcomas.

However, I believe that the type of Hodgkin's disease which is characterized by a febrile course and granulomatous lesions with many eosinophilic cells, pleomorphic infiltrate and many Sternberg giant cells, represents a disease sui generis and that the day will come when this differentiation will be of great practical importance.

There exists impressive evidence that this type of Hodgkin's disease may represent a genuine granulomatous lesion.

Misleading Experiences

A few words should be devoted to the misleading appearances of the various lymph node biopsies, especially the first biopsy which showed a

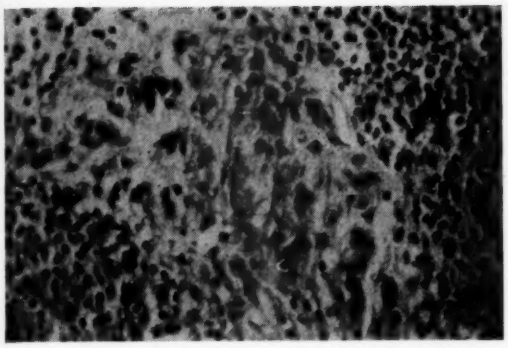

Figure 1. First surgical specimen, non-specific granuloma.

non-specific granulomatous reaction which even showed the presence of Langhan's giant cells (Fig. 1). It is very hard to decide, even retrospectively, whether or not this lymph node was affected by Hodgkin's disease.

We know from studying the lymph nodes adjacent to malignant tumors that they will react with non-specific granulomatous reaction.

Several pathologists to whom I have showed these lymph nodes feel that they represent an incidental finding but were not part of the disease.

Be that as it may, the second lymph node definitely showed the presence of a malignant lymphomatous process. Whether or not the bone lesions were actually part of the picture and can be explained by the extensive dissemination of the disease in the bone marrow I do not know.

Unfortunately, the biopsies from the bone marrow during the life of the patient did not show the nodules which were so amply present at autopsy.

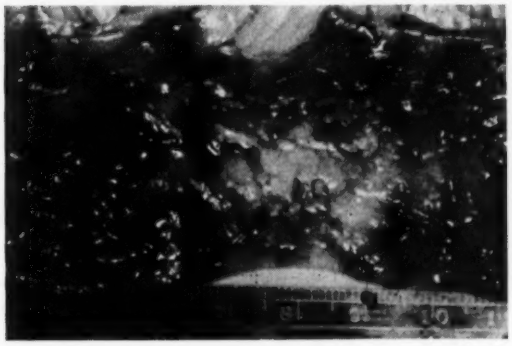

Figure 2. Autopsy, small intestine lymphoid hyperplasia.

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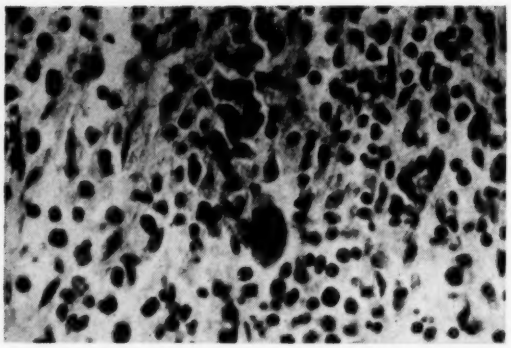

Figure 3. Microscopic intestine, typical Hodgkin's lesion.

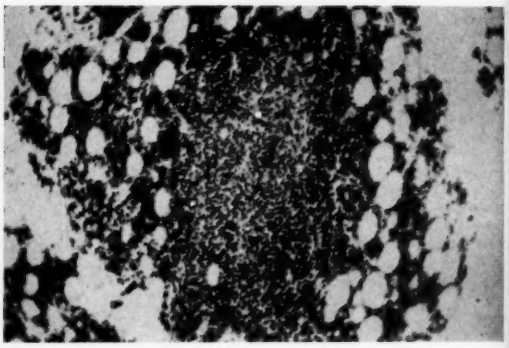

Figure 4. Bone marrow, replacement by Hodgkin's tissue.

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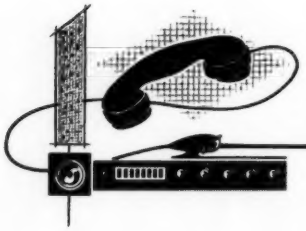

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